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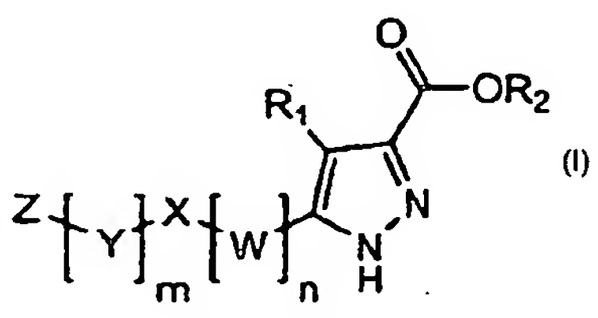
(54) **Title:** 5-SUBSTITUTED 2H-PYRAZOLE-3-CARBOXYLIC ACID DERIVATIVES AS AGONISTS FOR THE NICOTINIC ACID RECEPTOR RUP25 FOR THE TREATMENT OF DYSLIPIDEMIA AND RELATED DISEASES



(I)

(57) **Abstract:** The present invention relates to certain pyrazole carboxylic acid and ester derivatives, and pharmaceutically acceptable salts thereof, which exhibit useful pharmaceutical properties, for example as agonists for the RUP25 receptor. (I) Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the prophylaxis or treatment of metabolic-related disorders, including dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, Syndrome-X and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of α -glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers and the like.the substituents are defined in claim 1.

5-SUBSTITUTED 2H-PYRAZOLE-3-CARBOXYLIC ACID DERIVATIVES AS AGONISTS FOR THE NICOTINIC ACID RECEPTOR RUP25 FOR THE TREATMENT OF DYSLIPIDEMIA AND RELATED DISEASES

FIELD OF THE INVENTION

The present invention relates to certain pyrazole carboxylic acid and ester derivatives, and pharmaceutically acceptable salts thereof, which exhibit useful pharmaceutical properties, for example as agonists for the nicotinic acid receptor, refered to as **RUP25** herein. Also provided by the present invention are pharmaceutical compositions containing one or more compounds of the invention, and methods of using the compounds and compositions of the invention in the prophylaxis or treatment of metabolic-related disorders, including dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, Syndrome-X and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of α-glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers, thiazolidinedione and the like.

BACKGROUND OF THE INVENTION

Compounds of the invention as Antilipolytic Agents

Atherosclerosis and stroke are the numbers one and number three leading causes of death of both men and women in the United States. Type 2 diabetes is a public health problem that is serious, widespread and increasing. Elevated levels of low density lipoprotein (LDL) cholesterol or low levels of high density lipoprotein (HDL) cholesterol are, independently, risk factors for atherosclerosis and associated cardiovascular pathologies. In addition, high levels of plasma free fatty acids are associated with insulin resistance and type 2 diabetes. One strategy for decreasing LDL-cholesterol, increasing HDL-cholesterol, and decreasing plasma free fatty acids is to inhibit lipolysis in adipose tissue. This approach involves regulation of hormone sensitive lipase, which is the rate-limiting enzyme in lipolysis. Lipolytic agents increase cellular levels of cAMP, which leads to activation of hormone sensitive lipase within adipocytes. Agents that lower intracellular cAMP levels, by contrast, would be antilipolytic.

It is also worth noting in passing that an increase in cellular levels of cAMP down-regulates the secretion of adiponectin from adipocytes [Delporte, ML et al. *Biochem J* (2002) July]. Reduced levels of plasma adiponectin have been associated with metabolic-related disorders, including atherosclerosis, coronary heart disease, insulin resistance and type 2

diabetes [Matsuda, M et al. J Biol Chem (2002) July and reviewed therein].

Nicotinic acid (niacin, pyridine-3-carboxylic acid) is a water-soluble vitamin required by the human body for health, growth and reproduction; a part of the Vitamin B complex. Nicotinic acid is also one of the oldest used drugs for the treatment of dyslipidemia. It is a valuable drug in that it favorably affects virtually all of the lipid parameters listed above [Goodman and Gilman's Pharmacological Basis of Therapeutics, editors Harmon JG and Limbird LE, Chapter 36, Mahley RW and Bersot TP (2001) pages 971-1002]. The benefits of nicotinic acid in the treatment or prevention of atherosclerotic cardiovascular disease have been documented in six major clinical trials [Guyton JR (1998) Am J Cardiol 82:18U-23U]. Nicotinic acid and related derivatives, such as, acipimox have recently been discussed [Lorenzen, A et al (2001) Molecular Pharmacology 59:349-357].

Nicotinic acid and currently existing analogs thereof inhibit the production and release of free fatty acids from adipose tissue, likely via an inhibition of adenylyl cyclase, a decrease in intracellular cAMP levels, and a concomitant decrease in hormone sensitive lipase activity. Agonists that down-regulate hormone sensitive lipase activity leading to a decrease in plasma free fatty acid levels are likely to have therapeutic value. The consequence of decreasing plasma free fatty acids is two-fold. First, it will ultimately lower LDL-cholesterol and raise HDL-cholesterol levels, independent risk factors, thereby reducing the risk of mortality due to cardiovascular incidence subsequent to atheroma formation. Second, it will provide an increase in insulin sensitivity in individuals with insulin resistance or type 2 diabetes.

The rational development of novel, nicotinic acid receptor agonists that have fewer side-effects will be valuable, but to date this has been hindered by the inability to molecularly identify the nicotinic acid receptor. Furthermore, other receptors of the same class may exist on the surface of adipocytes and similarly decrease hormone sensitive lipase activity through a reduction in the level of intracellular cAMP but without the elicitation of adverse effects such as flushing, thereby representing promising novel therapeutic targets. Recent work suggests that nicotinic acid probably acts through a specific GPCR [Lorenzen A, et al. (2001) Molecular Pharmacology 59:349-357 and reviewed therein]. Further work has suggested that the effects of nicotinic acid on macrophages, spleen and probably adipocytes are mediated via this specific GPCR [Lorenzen A, et al. (2002) Biochemical Pharmacology 64:645-648 and reviewed therein].

Unfortunately, the use of nicotinic acid as a therapeutic agent is partially limited by a number of associated, adverse side-effects. These include flushing, free fatty acid rebound, and liver toxicity. The most noticeable side-effect associated with nicotinic acid is flushing. An individual may develop a visible, uncomfortable, hot or flushed feeling following each dose. Accordingly, there is a need for compounds and compositions with improved

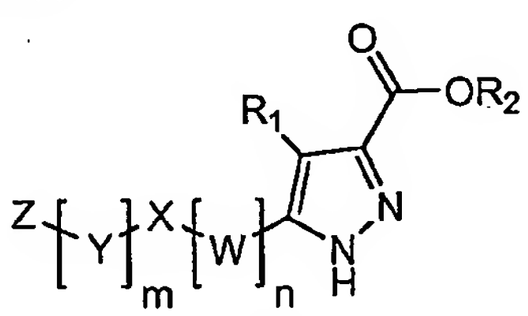
therapeutic activity with minimal side effects.

This application is related to US Provisional Patent Application, Serial No. 60/478,664, incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

The present invention is drawn to compounds which bind to and modulate the activity of a GPCR referred to herein as RUP25, and uses thereof. The term RUP25 as used herein includes the human sequences found in GeneBank accession number NP_808219, naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof.

One aspect of the present invention encompasses pyrazole carboxylic acid and ester derivatives as shown in Formula (I):



(I)

wherein:

W and Y are independently a straight or branched chain C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl or C_{1-4} alkoxy;

X is $-NR_3C(O)-$, $-C(O)NR_3$, $-NR_3S(O)_2-$, $-S(O)_2NR_3-$, $-NR_3C(O)NR_4-$, $-NR_3C(O)O-$, $-OC(O)NR_3-$, $-NR_3-$, $-C(O)-$, $-CH(OH)-$, $-C(NH)-$, $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

R_3 and R_4 are independently H, C_{1-4} alkyl, phenyl or heteroaryl, wherein each of the alkyl, phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

Z is H, halogen, phenyl or heteroaryl, wherein said phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxy, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

R_1 is H, hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R_2 is H or C_{1-8} alkyl and

"n" and "m" are each independently 0 or 1; or

a pharmaceutically acceptable salt, solvate or hydrate thereof;

provided that when X is $-NR_3-$ then "n" is 1.

One aspect of the present invention encompasses pharmaceutical compositions comprising at least one compound according to Formula (I), as described herein. In some embodiments, the pharmaceutical composition further comprises one or more agents selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

One embodiment of the present invention pertains to pharmaceutical compositions comprising a α-glucosidase inhibitor. In some embodiments the α-glucosidase inhibitor is acarbose, voglibose or miglitol. In some embodiments the α-glucosidase inhibitor is voglibose.

One embodiment of the present invention pertains to pharmaceutical compositions comprising an aldose reductase inhibitor. In some embodiments the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil.

One embodiment of the present invention pertains to pharmaceutical compositions comprising a biguanide. In some embodiments the biguanide is phenformin, metformin or buformin. In some embodiments the biguanide is metformin.

One embodiment of the present invention pertains to pharmaceutical compositions comprising a HMG-CoA reductase inhibitor. In some embodiments the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

One embodiment of the present invention pertains to pharmaceutical compositions comprising a fibrate. In some embodiments the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate.

One embodiment of the present invention pertains to pharmaceutical compositions comprising an angiotensin converting enzyme inhibitor. In some embodiments the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril.

One embodiment of the present invention pertains to pharmaceutical compositions comprising an insulin secretion enhancer. In some embodiments the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide;

glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide.

One embodiment of the present invention pertains to pharmaceutical compositions comprising a thiazolidinedione. In some embodiments the thiazolidinedione is rosiglitazone or pioglitazone. In some embodiments the thiazolidinedione is rosiglitazone.

One aspect of the present invention pertains to a compound of Formula (I), as described herein, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to a compound of Formula (I), as described herein, for use in a method of prophylaxis or treatment of a metabolic-related disorder of the human or animal body by therapy.

One aspect of the present invention pertains to methods for prophylaxis or treatment of a metabolic-related disorder in an individual in need of prophylaxis or treatment comprising administering to the individual a therapeutically effective amount of a compound according of Formula (I), as described, or a pharmaceutical composition.

One aspect of the present invention pertains to methods of modulating a RUP25 receptor in an individual comprising contacting the receptor with a compound according Formula (I). In some embodiments the compound is an agonist. In some embodiments the modulation of the RUP25 receptor is for prophylaxis or treatment of a metabolic-related disorder in an individual in need of said prophylaxis or treatment.

One embodiment of the present invention relates to methods of prophylaxis or treatment of metabolic-related disorders. In some embodiments the metabolic-related disorder is of the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes. In some embodiments the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes. In some embodiments the metabolic-related disorder is dyslipidemia. In some embodiments the metabolic-related disorder is atherosclerosis. In some embodiments the metabolic-related disorder is coronary heart disease. In some embodiments the metabolic-related disorder is insulin resistance. In some embodiments the metabolic-related disorder is type 2 diabetes.

One aspect of the present invention encompasses compounds of Formula (I) for production of a medicament for use in prophylaxis or treatment of a metabolic-related disorder. In some embodiments, the use of a compound of Formula (I) for production of a medicament further comprises one or more agents selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor,

squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione. In some embodiments the agent is a α-glucosidase inhibitor. In some embodiments the α-glucosidase inhibitor is acarbose, voglibose or miglitol. In some embodiments the α-glucosidase inhibitor is voglibose. In some embodiments the agent is an aldose reductase inhibitor. In some embodiments the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil. In some embodiments the agent is a biguanide. In some embodiments the biguanide is phenformin, metformin or buformin. In some embodiments the biguanide is metformin. In some embodiments the agent is a HMG-CoA reductase inhibitor. In some embodiments the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin. In some embodiments the agent is a fibrate. In some embodiments the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate. In some embodiments the agent is an angiotensin converting enzyme inhibitor. In some embodiments the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril. In some embodiments the agent is an insulin secretion enhancer. In some embodiments the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide. In some embodiments the agent is a thiazolidinedione. In some embodiments the thiazolidinedione is rosiglitazone or pioglitazone. In some embodiments the thiazolidinedione is rosiglitazone. In some embodiments the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes. In some embodiments the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes. In some embodiments the metabolic-related disorder is dyslipidemia. In some embodiments the metabolic-related disorder is atherosclerosis. In some embodiments the metabolic-related disorder is coronary heart disease. In some embodiments the metabolic-related disorder is insulin resistance. In some embodiments the metabolic-related disorder is type 2 diabetes.

One aspect of the present invention encompasses a method of producing a pharmaceutical composition comprising admixing at least one compound according to

Formula (I), as described herein, and a pharmaceutically acceptable carrier or excipient.

Applicant reserves the right to exclude any one or more of the compounds from any of the embodiments of the invention. Applicant additionally reserves the right to exclude any metabolic-related disorder from any of the embodiments of the invention.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Figure 1 depicts a histogram representing relative expression levels of **hRUP25** detected in different human tissues *via* DNA microarray. The horizontal axis displays the different tissues, identified in vertical text above the bar. The vertical axis indicates level of expression of **hRUP25**. In Figure 1, note the high level of expression in primary adipocytes of **hRUP25** (designated by the symbol " * ").

Figure 2. Figure 2 depicts melanophores transfected with DNA plasmids expressing **hRUP25** without treatment. These cells are pigment-aggregated because **hRUP25** are Gi-coupled receptors having a high basal level of activity, and therefore driving the aggregation to a measurable level in the absence of a ligand.

Figures 3A-B. Figures 3A and 3B illustrate the dose-dependant, nicotinic acid induced aggregation response of melanophores transfected with increasing amounts of plasmid DNA encoding **hRUP25** (Figure 3A). Cells transfected with 10μg of plasmid DNA encoding **hRUP25**, respond to nicotinic acid with an EC_{50} of about 54nM.

As negative controls, Figure 3B depicts melanophores transfected with either salmon sperm DNA (Mock) or plasmid DNA encoding the α_{2A}AR. As is evident there is no aggregation response in these cells upon nicotinic acid treatment at doses up to 10μM.

Figure 4. Figure 4 illustrates the nicotinic acid induced-inositol phosphates (IPs) accumulation in HEK293 cells co-expressing **hRUP25** and the chimeric Gαq-subunit in which the last five amino acids have been replaced with the corresponding amino acids of Gαi (GqΔGi). This construct has been shown to convert the signaling of a Gi-coupled receptor to the Gq pathway (i.e. accumulation of inositol phosphates) in response to receptor activation. Cells transfected with GqΔGi plus either empty plasmid or the constitutively activated α_{2A}AR (α_{2A}K) served as controls for the IP assay which are non-responsive to nicotinic acid.

Figure 5A. Figure 5A is a set of immunofluorescent photomicrographs illustrating the expression of hemaglutinin (HA)-tagged **hRUP25** in a stably transfected line of CHO cells (top; clone #46). No significant labeling is detected in mock stably-transfected CHO cells (Mock). The lower panels identify the nuclear (DAPI) staining of cells in the same field.

Figure 5B. Figure 5B illustrates nicotinic acid and nicotine induced-inhibition of forskolin stimulated cAMP accumulation in **hRUP25**-CHO cell stable line #46 (described in preceding paragraph). The EC_{50} for nicotinic acid is 23.6nM and that for nicotine is 9.8μM.

Figure 6. Figure 6 indicates that, in response to nicotinic acid, both **hRUP25** and the mouse ortholog **mRUP25** can inhibit TSHR stimulated cAMP production (in the presence and absence of TSH).

Figure 7. Figure 7 shows the saturation binding curves of [^{3}H]nicotinic acid ([^{3}H]NA) to membranes prepared from HEK293 cells transiently expressing either **hRUP25** or **mRUP25.** Note the significant binding of [^{3}H]NA relative to either that found in membranes derived from mock transfected cells or in the presence of an excess of non-labeled nicotinic acid (200μM).

Figure 8. Figure 8 is a table comparing the rank order of potency of various compounds on **hRUP25** and the pharmacologically defined nicotinic acid receptor. The potencies at **hRUP25** derived both by a functional analysis measuring the inhibition of forskolin induced cAMP production and competitive radioligand binding assays, closely match the order of potencies of the pharmacologically defined nicotinic acid receptor.

Figures 9A-B. Figure 9A depicts nicotinic acid and related compounds inhibiting isoproterenol induced lipolysis in rat epidimal fat derived adipocytes at a concentration of 10μM. P-3-T represents 3-tetrazole-5-pyridine. **Figure 9B** illustrates a nicotinic acid dose-dependent inhibition of isoproterenol induced-lipolysis in rat epidimal fat derived adipocytes. Note the rightward shift in the dose-response curves with increasing concentrations of nicotinic acid.

Figure 10. Figure 10 illustrates the ability of both nicotinic acid and the related compound P-3-T (3-tetrazole-5-pyridine) to inhibit isoproterenol induced lipolysis in adipocyte primary cultures derived from human subcutaneous fat in a dose-dependant manner. The EC_{50} value for nicotinic acid and P-3-T were 716nM and 218nM respectively.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AFFINITY REAGENTS shall mean compounds that specifically and measurably bind to a target molecule. Preferably the target molecule is a GPCR of the invention.

Preferably the AFFINITY REAGENTS are labeled to facilitate detection.

AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate an intracellular response when they bind to the receptor. In some embodiments, AGONISTS are those materials not previously known to activate the intracellular response when they bind to the receptor (*e.g.* to enhance GTPγS binding to membranes or to lower intracellular cAMP level). In some embodiments, AGONISTS are those materials not previously known to inhibit lipolysis when they bind to the receptor.

ALLOSTERIC MODULATORS shall mean materials (*e.g.*, ligands, candidate compounds) that affect the functional activity of the receptor but which do not inhibit the endogenous ligand from binding to the receptor. Allosteric modulators include inverse agonists, partial agonists and agonists.

ANTAGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that competitively bind to the receptor at the same site as the agonists but which do not activate an intracellular response, and can thereby inhibit the intracellular responses elicited by agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist. In some embodiments, ANTAGONISTS are those materials not previously known to compete with an agonist to inhibit the cellular response when they bind to the receptor, *e.g.* wherein the cellular response is GTPγS binding to membranes or to the lowering of intracellular cAMP level.

ANTILIPOLYTIC GPCR shall mean a GPCR expressed by adipocytes and coupled to Gi or a Gi-coupled GPCR belonging to the nicotinic acid receptor sub-family of GPCRs. Activation of a Gi-coupled GPCR on adipocytes lowers intracellular cAMP levels, resulting in an inhibition of hormone sensitive lipase activity.

ATHEROSCLEROSIS is intended herein to encompass disorders of large and medium-sized arteries that result in the progressive accumulation within the intima of smooth muscle cells and lipids.

CHEMICAL GROUP, MOIETY or RESIDUE shall have the following meaing in the specification and Formulae described herein:

The term "**C_{1-5} alkylene**" refers to a divalent branched or straight carbon group consisting of 1 to 5 carbon atoms, such as, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2CH_2CH_2CH_2-$, and the like. In some embodiments the "**C_{1-5} alkylene**" group contains one double bond, one triple bond or a carbonyl group whereby the one single bond of the "**C_{1-5} alkylene**" group is replaced by a double bond or triple bond, such as, $-CH=CH-$, $-C(CH_3)=CH-$, $-CH=C(CH_3)-$, $-CH_2CH=CH-$, $-CH_2CH_2CH=CH-$, $-CH=CHCH_2CH_3-$, and the like, when a double bond is present it can be *cis*, *trans* or a mixture of both. In some

embodiments, one carbon of the "**C_{1-5} alkylene**" group is the carbon of a carbonyl group, such as, -C(O)-, -CH_2C(O)-, -C(O)CH_2-, -C(O)CH(CH_3)-, and the like.

The term "**C_{2-4} alkenyl**" denotes a radical containing 2 to 4 carbons and at least one double bond. Some embodiments have 2 carbons. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl and the like. Furthermore, the term "**alkenyl**" includes pure *cis* and *trans* isomers as well as mixtures thereof.

The term "**C_{1-4} alkoxy**" as used herein denotes a radical alkyl, defined above, attached directly to an oxygen atom such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy and the like.

The term "**C_{1-8} alkyl**" denotes a radical containing 1 to 8 carbons unless otherwise specified. Some embodiments are 1 to 6 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, some embodiments are 1 to 2 carbons, and some embodiments have 1 carbon. Examples of an alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl and the like.

The term "**C_{1-4} alkylamino**" denotes an amino substituted with one group selected from alkyl containing 1 to 4 carbon atoms. Some examples include methylamino, ethylamino, and the like.

The term "**di-C_{1-4}-alkylamino**" denotes an amino substituted with two alkyl radicals that can be same or different wherein the alkyls group can contain 1 to 4 carbon atoms. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

The term "**C_{2-4} alkynyl**" denotes a radical containing 2 to 4 carbons and at least one triple bond. Some embodiments have 2 carbons. Examples of an alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl and the like.

The term "**C_{1-4} alkylsulfinyl**" denotes a sulfoxide, i.e., -S(O)-, radical containing 1 to 4 carbons, linear or branched. Examples include methylsulfinyl, ethylsulfinyl and the like.

The term "**C_{1-4} alkylsulfonyl**" denotes a sulfone, i.e., -$S(O)_2$-, radical containing 1 to 4 carbons, linear or branched. Examples include methylsulfonyl, ethylsulfonyl and the like.

The term "**C_{1-4} alkylthio**" denotes a sulfide, i.e., -S-, radical containing 1 to 4 carbons, linear or branched. Examples include methylsulfide, ethylsulfide, isopropylsulfide and the like.

The term "**amino**" denotes the group –NH_2.

The term "**cyano**" denotes the group –CN.

The term "**halo**" or "**halogen**" denotes to a fluoro, chloro, bromo or iodo group.

The term "**C_{1-4} haloalkoxy**" denotes a haloalkyl, as defined above, that is directly attached to an oxygen to form a difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**C_{1-4} haloalkyl**" denotes an alkyl group as defined above that is substituted with one or more halogens, preferably fluorine, such as a fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "**C_{1-4} haloalkylsulfinyl**" denotes a sulfoxide, i.e., -S(O)-, radical containing 1 to 4 carbons substituted with one or more halogens, linear or branched. Examples include trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "**C_{1-4} haloalkylsulfonyl**" denotes a sulfone, i.e., -$S(O)_2$-, radical containing 1 to 4 carbons, linear or branched substituted with one or more halogens. Examples include trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "**C_{1-4} haloalkylthio**" denotes an alkylthio radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "**heteroaryl**" denotes 5 or 6-membered aromatic rings having at least 1, 2, 3 or 4 heteroatoms in the ring, examples include, but are limited to, 1,3,4-oxadiazole, 1,2,4-oxadiazole, triazole, pyrazole, pyrole, isoxazole, furane, thiophene, thiazole, oxazole, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, and the like; in some embodiments the "**heteroaryl**" is further substituted with substituents as described herein.

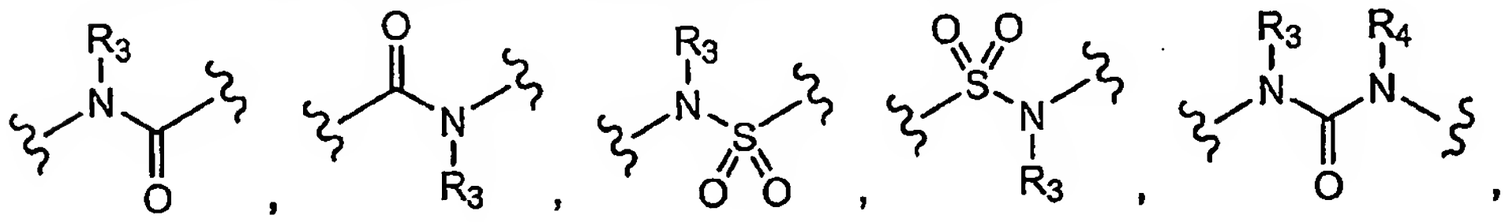
The term "**hydroxyl**" denotes the group –OH.

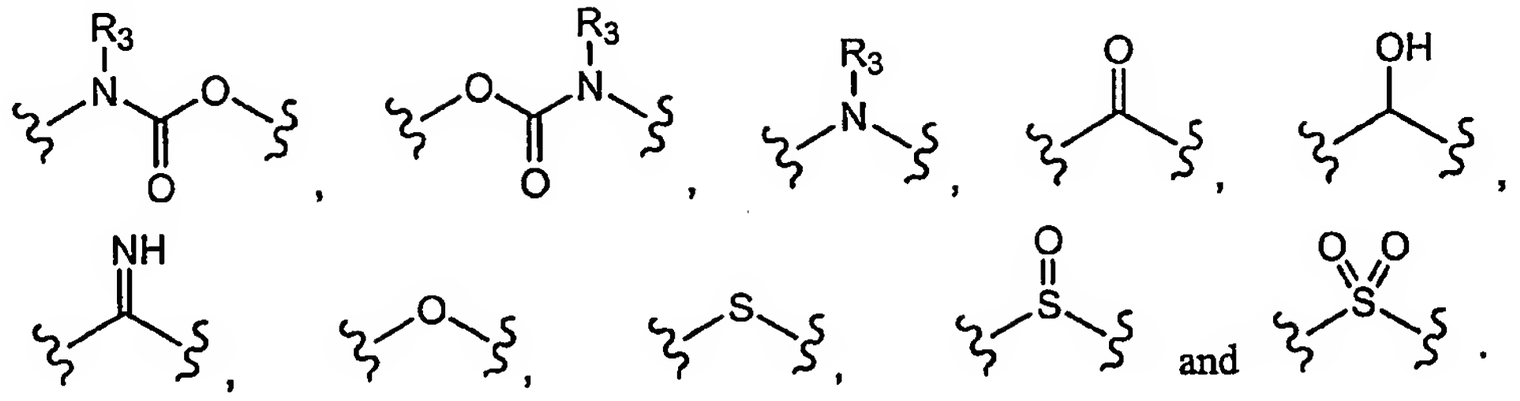
The term "**nitro**" denotes the group –NO_2.

The term "**phenyl**" denotes the C_6H_5- group, in some embodiments the "**phenyl**" is further substituted with substituents as described herein.

The term "**thiol**" denotes the group –SH.

The variable "**X**" in the Formulae found in this disclosure is selected from the group consisting of -$NR_3C(O)$-, -$C(O)NR_3$, -$NR_3S(O)_2$-, -$S(O)_2NR_3$-, -$NR_3C(O)NR_4$-, -$NR_3C(O)O$-, -$OC(O)NR_3$-, -NR_3-, -C(O)-, -CH(OH)-, -C(NH)-, -O-, -S-, -S(O)- and - $S(O)_2$- and are represented respectively by the following:





COMPOSITION means a material comprising at least one component; a "pharmaceutical composition" is an example of a composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality; i.e. the ability to activate/inhibit a signal transduction pathway, in contrast to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example section of this patent document.

COMPRISING, CONSISTING ESSENTIALLY OF, and **CONSISTING OF** are defined herein according to their standard meaning. A defined meaning set forth in the M.P.E.P. controls over a defined meaning in the art and a defined meaning set forth in controlling Federal Circuit case law controls over a meaning set forth in the M.P.E.P.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" a RUP25 receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a RUP25 receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a RUP25 receptor.

CORONARY HEART DISEASE is intended herein to encompass disorders comprising a narrowing of the small blood vessels that supply blood and oxygen to the heart. CORONARY HEART DISEASE usually results from the build up of fatty material and plaque. As the coronary arteries narrow, the flow of blood to the heart can slow or stop. CORONARY HEART DISEASE can cause chest pain (stable angina), shortness of breath, heart attack, or other symptoms.

DECREASE is used to refer to a reduction in a measurable quantity and is used synonymously with the terms "reduce", "diminish", "lower", and "lessen".

DIABETES as used herein is intended to encompass the usual diagnosis of DIABETES made from any of the methods including, but not limited to, the following list: symptoms of diabetes (*e.g.*, polyuria, polydipsia, polyphagia) plus casual plasma glucose levels of greater than or equal to 200 mg/dl, wherein casual plasma glucose is defined any time of the day regardless of the timing of meal or drink consumption; 8 hour fasting plasma glucose levels of less than or equal to 126 mg/dl; and plasma glucose levels of greater than or equal to 200 mg/dl 2 hours following oral administration of 75 g anhydrous glucose dissolved

in water.

DISORDERS OF LIPID METABOLISM are intended herein to include, but not be limited to, dyslipidemia.

DYSLIPIDEMIA is intended herein to encompass disorders comprising any one of elevated level of plasma free fatty acids, elevated level of plasma cholesterol, elevated level of LDL-cholesterol, reduced level of HDL-cholesterol, and elevated level of plasma triglycerides.

IN NEED OF PROPHYLAXIS OR TREATMENT as used herein refers to a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from prophylaxis or treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will be ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. In general, "in need of prophylaxis" refers to the judgment made by the caregiver that the individual will become ill. In this context, the compounds of the invention are used in a protective or preventive manner. However, "in need of treatment" refers to the judgment of the caregiver that the individual is already ill, therefore, the compounds of the present invention are used to alleviate, inhibit or ameliorate the disease, condition or disorder.

INDIVIDUAL as used herein refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INSULIN RESISTANCE as used herein is intended to encompass the usual diagnosis of insulin resistance made by any of a number of methods, including but not restricted to: the intravenous glucose tolerance test or measurement of the fasting insulin level. It is well known that there is an excellent correlation between the height of the fasting insulin level and the degree of insulin resistance. Therefore, one could use elevated fasting insulin levels as a surrogate marker for insulin resistance for the purpose of identifying which normal glucose tolerance (NGT) individuals have insulin resistance. A diagnosis of insulin resistance can also be made using the euglycemic glucose clamp test.

INVERSE AGONISTS shall mean materials (*e.g.*, ligand, candidate compound) that bind either to the endogenous form or to the constitutively activated form of the receptor so as to reduce the baseline intracellular response of the receptor observed in the absence of agonists.

KNOWN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

LIGAND shall mean a molecule specific for a naturally occurring receptor.

METABOLIC-RELATED DISORDERS are intended herein to include, but not be limited to, dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

As used herein, the terms **MODULATE** or **MODIFY** are meant to refer to an increase or decrease in the amount, quality, or effect of a particular activity, function or molecule.

As used herein, the term **NICOTINIC ACID ANALOG OR DERIVATIVE** is meant to molecules which bind to nicotinic acid receptors and have substantially similar effects on the receptor. Such analogs and derivatives are well-known to those skilled in the art and include, but are not limited to, acipimox and niacinamide.

PARTIAL AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do full agonists.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

STIMULATE or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

SUBJECT shall mean primates, including but not limited to humans and baboons, as well as pet animals such as dogs and cats, laboratory animals such as rats and mice, and farm animals such as horses, sheep, and cows.

SUBSTANTIALLY shall refer to a result which is within 40% of a control result, preferably within 35%, more preferably within 30%, more preferably within 25%, more preferably within 20%, more preferably within 15%, more preferably within 10%, more preferably within 5%, more preferably within 2%, and most preferably within 1% of a control result. For example, in the context of receptor functionality, a test receptor may exhibit substantially similar results to a control receptor if the transduced signal, measured using a method taught herein or similar method known to the art-skilled, is within 40% of the signal produced by a control signal.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

THERAPEUTICALLY EFFECTIVE AMOUNT as used herein refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

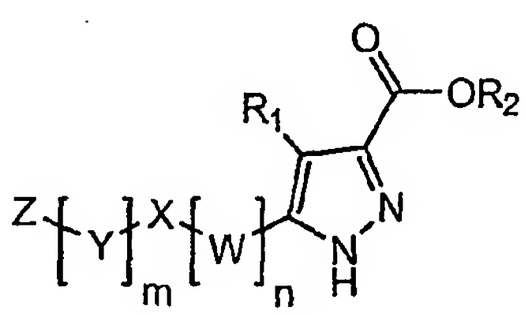
(1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that can be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and

(3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

COMPOUNDS OF THE INVENTION

One aspect of the present invention encompasses pyrazole carboxylic acid and ester derivatives as shown in Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein Z, Y, X, W, m, n, R_1, and R_2 have the same definitions as described herein, *supra* and *infra*.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or

group. When a chemical group herein is "substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, "substituted with one or more substituents" refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

It is understood and appreciated that compounds of the invention may have one or more chiral centers, and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including, but not limited to, racemates. Accordingly, some embodiments of the present invention pertain to compounds of Formula (**I**) and formulae used throughout this disclosure that are *R* enantiomers. Further, some embodiments of the present invention pertain to compounds of Formula (**I**) and formulae used throughout this disclosure that are *S* enantiomers. When more than one chiral center is present, for example two chiral centers then, some embodiments of the present invention include compounds that are *RS* or *SR* enantiomers. In further embodiments, compounds of the present invention are *RR* or *SS* enantiomers. It is understood that compounds of Formula (**I**) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers, and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

In some embodiments, when both R_1 and R_2 are H then $-[W]_n$-X-$[Y]_m$-Z together is not CO_2H, C(O)-C_6H_4-*p*-O-C_8H_{17}, OCH_2CH_3, OH, $CH_2CH_2CH_2CH_2CO_2H$, $CH_2CH_2CH_2CO_2H$, CH_2CO_2H and $CH_2CH_2CO_2H$.

In some embodiments, when R_1 is CH_3 and R_2 is H then $-[W]_n$-X-$[Y]_m$-Z together is not CH_2CO_2H, C(O)CH=CH C_6H_5, C(O)C_6H_4-*p*-OCH_3, CO_2H, C(O)CH_3, C(O)C_6H_4-*o*-CH_3, C(O)C_6H_4-*o*-Br, C(O)C_6H_4-*o*-Cl, and C(O)C_6H_5.

In some embodiments, when R_1 is Br and R_2 is H then $-[W]_n$-X-$[Y]_m$-Z together is not CO_2H.

In some embodiments, when R_1 is OH and R_2 is H then $-[W]_n-X-[Y]_m-Z$ together is not CO_2H.

In some embodiments, when R_1 is H and R_2 is CH_3 then $-[W]_n-X-[Y]_m-Z$ together is not 2,6-dichloro-4-trifluoromethylphenoxy, $C(O)NH-C_6H_4-p-OCH_2CH_3$, $NHC(O)CH(CH_3)_2$, SCH_3, $C(O)-C_6H_4-p-O-C_8H_{17}$, SCH_2CH_3, $C(O)NHC_6H_5$, $CH(OCH_3)_2$, $CH_2OC(O)CH_3$, CO_2H, CO_2CH_3, $C(O)C_6H_4-p-NO_2$, $C(O)C_6H_5$, $CH_2CH_2CO_2CH_3$, $CH_2CH_2CH_2CH_2CO_2CH_3$, $CH_2CH_2CH_2CO_2CH_3$ and $CH_2CO_2CH_3$.

In some embodiments, when R_1 is OH and R_2 is CH_3 then $-[W]_n-X-[Y]_m-Z$ together is not $CH_2OCH_2C_6H_5$, $CH_2OCH(CH_3)_2$ and CH_2OH.

In some embodiments, when R_2 is CH_3 then:

R_1 is not CH_3 and $-[W]_n-X-[Y]_m-Z$ together is not 2,6-dichloro-4-trifluoromethylphenoxy;

R_1 is not I and $-[W]_n-X-[Y]_m-Z$ together is not $CO_2C(CH_3)_3$;

R_1 is not $C(CH_3)_3$ and $-[W]_n-X-[Y]_m-Z$ together is not formyl;

R_1 is not Br and $-[W]_n-X-[Y]_m-Z$ together is not CO_2CH_3; and

R_1 is not $CH_2CH_2CH_2CH_3$ and $-[W]_n-X-[Y]_m-Z$ together is not formyl.

In some embodiments, when R_1 is H and R_2 is CH_2CH_3 then $-[W]_n-X-[Y]_m-Z$ together is not $CH_2SCH_2CH_3$, $OCH_2CH_2CH=CH_2$, $CH_2CH_2CH_2OH$, CH_2CH_2CHO, $CO_2CH_2CH_3$, OCH_3, $C(O)CH_2Br$, $CO_2C_8H_{17}$, formyl, OH, $CH_2N(CH_2CH_2Cl)_2$, $CH(CH_3)OC(O)CH_3$, CH_2OH, $CH_2OC(O)CH_3$, $C(O)CH_3$, $C(O)C_6H_5$ and $C(O)NHCH_2CO_2CH_2CH_3$.

In some embodiments, when R_1 is CH_3 and R_2 is CH_2CH_3 then $-[W]_n-X-[Y]_m-Z$ together is not $CH(OH)C_6H_4-p-N(CH_3)_2$, $C(O)CH_2C(O)CH_3$, $CO_2CH_2C_6H_5$, CO_2CH_3, $C(O)CH_2CH_2CH_3$, $C(O)CH_3$, $C(O)C_6H_4-p-OCH_3$, $C(O)C_6H_4-o-Br$, $C(O)C_6H_4-p-Cl$, $C(O)C_6H_4-o-Cl$, $C(O)CH_2C_6H_5$ and $C(O)C_6H_5$.

In some embodiments, when R_2 is CH_2CH_3 then:

R_1 is not I and $-[W]_n-X-[Y]_m-Z$ together is not $CO_2CH_2CH_3$;

R_1 is not CF_3 and $-[W]_n-X-[Y]_m-Z$ together is not $CO_2CH_2CH_3$; and

R_1 is not Br and $-[W]_n-X-[Y]_m-Z$ together is not $CO_2CH_2CH_3$.

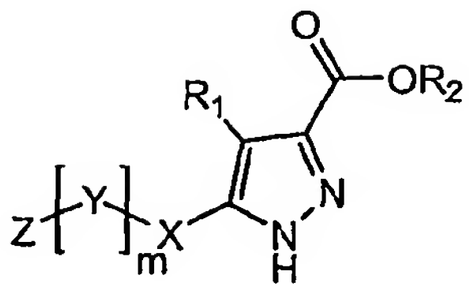
In some embodiments, when R_1 is OH and R_2 is CH_2CH_3 then $-[W]_n-X-[Y]_m-Z$ together is not $C(O)C_6H_5$, $C(O)NH_2$ and $CO_2CH_2CH_3$.

In some embodiments, when R_1 is H and R_2 is $C(CH_3)_3$ then $-[W]_n-X-[Y]_m-Z$ together is not $CO_2C(CH_3)_3$, $C(O)NHC(O)CH_3$ and $C(O)NH_2$.

In some embodiments, when R_1 is OH and R_2 is $CH_2CH_2CH_2CH_3$ then $-[W]_n-X-[Y]_m-Z$ together is not $C(O)C_6H_5$.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein "n" is 0. In some embodiments, compounds of the invention can be represented by

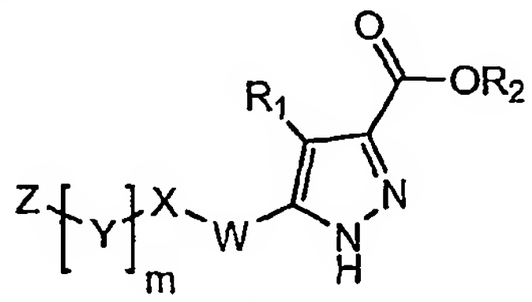
Formula (**Ia**) as illustrated below:



(**Ia**)

wherein each variable in Formula (**Ia**) has the same meaning as described herein, *supra* and *infra*.

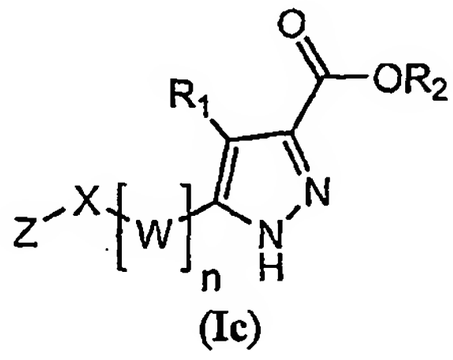
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein "n" is 1. In some embodiments, compounds of the invention can be represented by Formula (**Ib**) as illustrated below:



(**Ib**)

wherein each variable in Formula (**Ib**) has the same meaning as described herein, *supra* and *infra*.

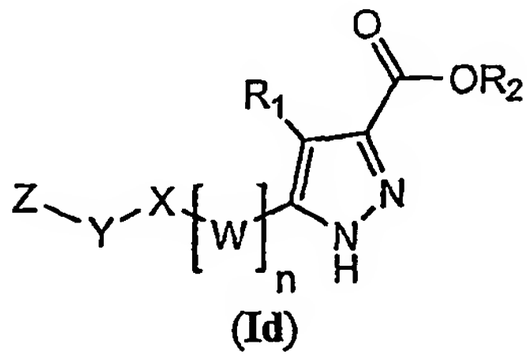
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein "m" is 0. In some embodiments, compounds of the invention can be represented by Formula (**Ic**) as illustrated below:



(**Ic**)

wherein each variable in Formula (**Ic**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein "m" is 1. In some embodiments, compounds of the invention can be represented by Formula (**Id**) as illustrated below:



(**Id**)

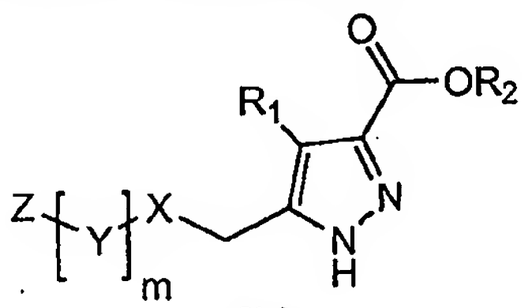
wherein each variable in Formula (**Id**) has the same meaning as described herein, *supra* and

infra.

Some embodiments of the present invention pertain to compounds of Formula (I), more specifically Formulae (**Ib**), (**Ic**) or (**Id**), wherein W is the straight or branched chain C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. The C_{1-5} alkylene group is a straight chain group of 1 to 5 carbons. In some embodiments the alkylene chain consists of single bonds. In some embodiments two adjacent carbons in this chain can be bonded together by a double bond or a triple bond, in still other embodiments, a single carbon can be bonded to an oxygen by a double bond thus forming a carbonyl group as represented in some embodiments disclosed herein [i.e., -C(=O)-].

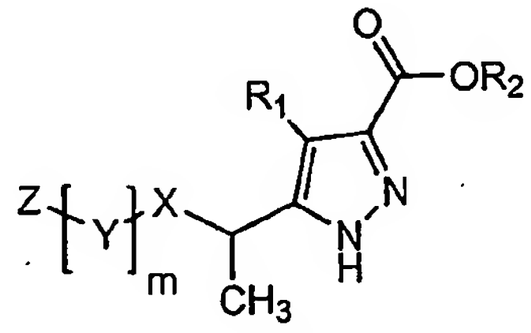
The C_{1-5} alkylene group, when present (i.e., n = 1), can be optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. The number of substituents on the C_{1-5} alkylene group depends on the specific group present, for example, when the C_{1-5} alkylene group is $-CH_2-$ the number of substituents can be 1 or 2. Whereas, when the C_{1-5} alkylene group is $-(CH_2)_4-$ then the number of substituents can range from 1 to 8.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein W is $-CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In one embodiment, W is $-CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**Ie**) as illustrated below:



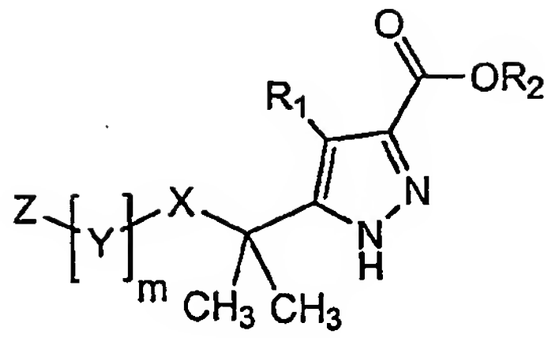
(**Ie**)

wherein each variable in Formula (**Ie**) has the same meaning as described herein, *supra* and *infra*. In some embodiments W is $-CH(CH_3)-$ optionally substituted with halogen, hydroxyl or C_{1-4} alkoxy. In one embodiment, W is $-CH(CH_3)-$. In some embodiments, compounds of the present invention can be represented by Formula (**If**) as illustrated below:



(**If**)

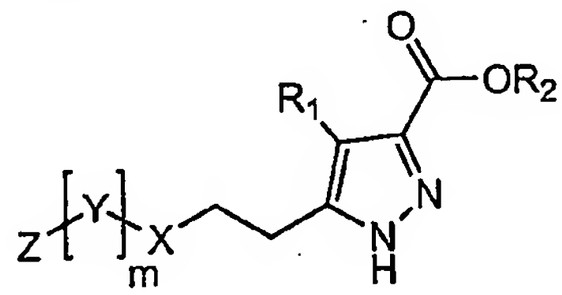
wherein each variable in Formula (**If**) has the same meaning as described herein, *supra* and *infra*. In some embodiments W is $-C(CH_3)_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**Ig**) as illustrated below:



(Ig)

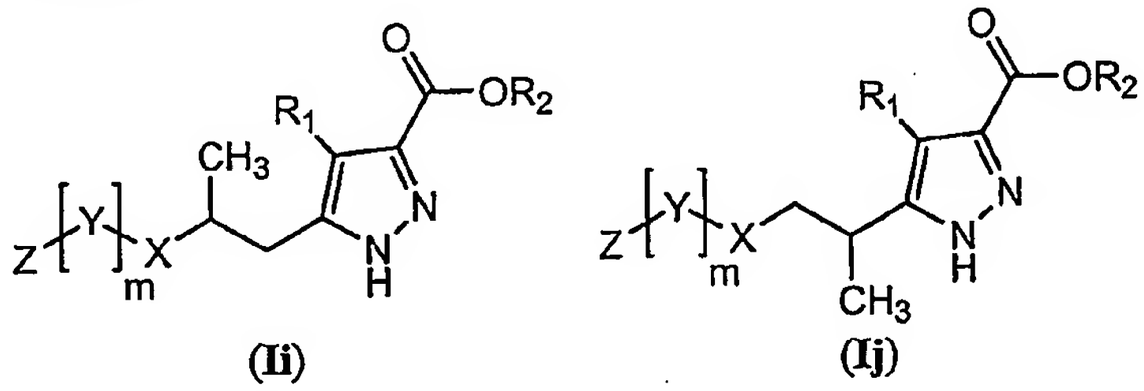
wherein each variable in Formula **(Ig)** has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein W is $-CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In one embodiment, W is $-CH_2CH_2-$. In some embodiments, compounds of the present invenetion can be represented by Formula **(Ih)** as illustrated below:



(Ih)

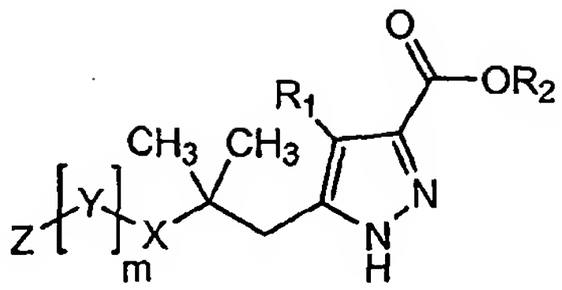
wherein each variable in Formula **(Ih)** has the same meaning as described herein, *supra* and *infra*. In some embodiments W is $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$. In some embodiments, compounds of the present invention can be represented by Formulae **(Ii)** and **(Ij)** respectively as illustrated below:



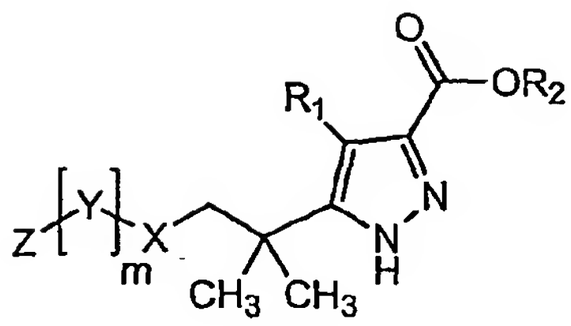
(Ii) **(Ij)**

wherein each variable in Formulae **(Ii)** and **(Ij)** has the same meaning as described herein, *supra* and *infra*.

In some embodiments W is $-C(CH_3)_2CH_2-$ or $-CH_2C(CH_3)_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-C(CH_3)_2CH_2-$ or $-CH_2C(CH_3)_2-$. In some embodiments, compounds of the present invention can be represented by Formulae **(Ik)** and **(Im)** respectively as illustrated below:



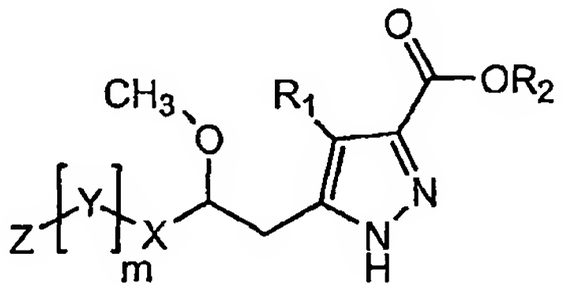
(Ik)



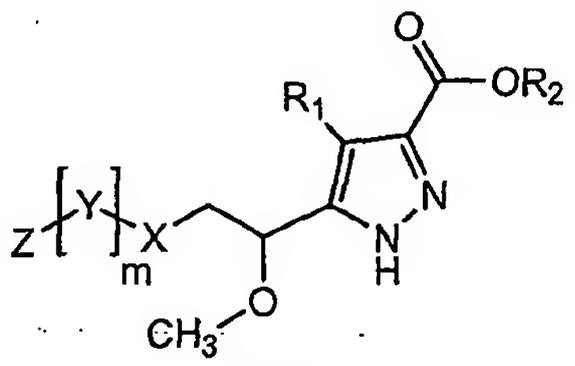
(Im)

wherein each variable in Formulae (**Ik**) and (**Im**) has the same meaning as described herein, *supra* and *infra*.

In some embodiments W is $-CH(OCH_3)CH_2-$ or $-CH_2CH(OCH_3)-$ optionally substituted with halogen, hydroxyl or C_{1-4} alkyl. In some embodiments W is $-CH(OCH_3)CH_2-$ or $-CH_2CH(OCH_3)-$. In some embodiments, compounds of the present invention can be represented by Formulae (**In**) and (**Io**) respectively as illustrated below:



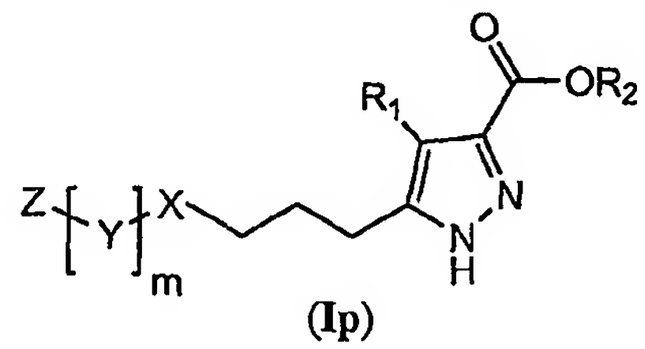
(In)



(Io)

wherein each variable in Formulae (**In**) and (**Io**) has the same meaning as described herein, *supra* and *infra*.

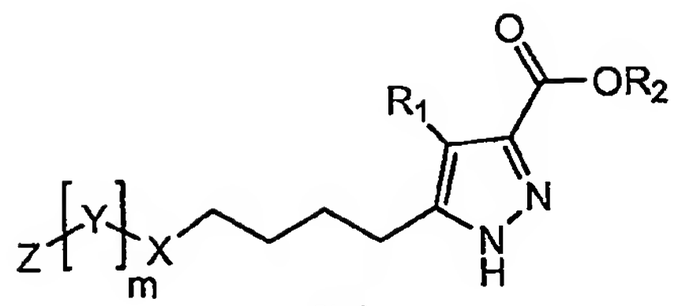
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is $-CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-CHClCH_2CH_2-$ or $-CH_2CH_2CHCl-$. In some embodiments W is $-CH_2CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**Ip**) as illustrated below:



(Ip)

wherein each variable in Formula (**Ip**) has the same meaning as described herein, *supra* and *infra*.

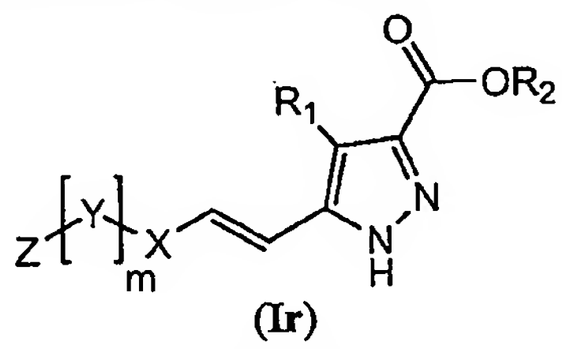
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is $-CH_2CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-CH_2CH_2CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**Iq**) as illustrated below:



(Iq)

wherein each variable in Formula (**Iq**) has the same meaning as described herein, *supra* and *infra*.

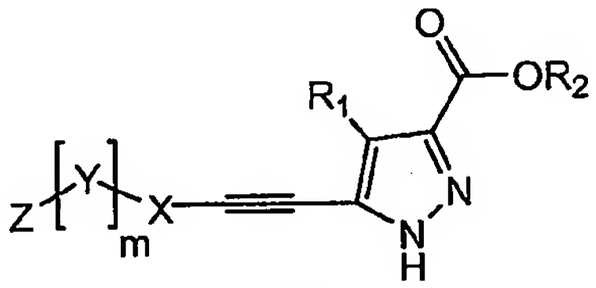
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -CH=CH- optionally substituted with C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is -CH=CH-. In some embodiments, compounds of the present invention can be represented by Formula (**Ir**) as illustrated below:



(Ir)

wherein each variable in Formula (**Ir**) has the same meaning as described herein, *supra* and *infra*. It is understood that when a double bond is present it can be either *cis* or *trans*; or a mixture of both *cis* and *trans*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -C≡C-. In some embodiments, compounds of the present invention can be represented by Formula (**Is**) as illustrated below:



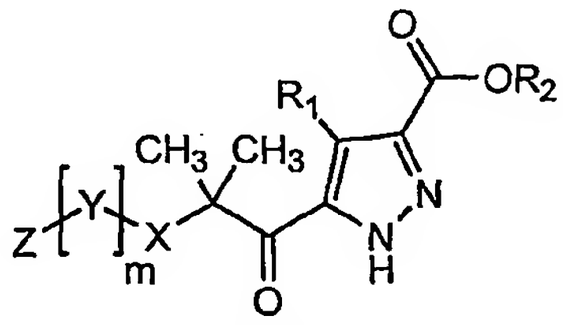
(Is)

wherein each variable in Formula (**Is**) has the same meaning as described herein, *supra* and *infra*.

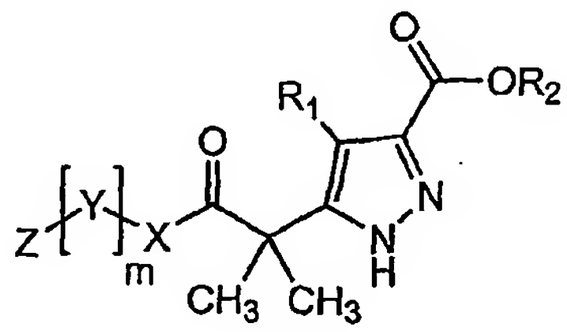
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -C(O)-. In some embodiments, W is -C(O)- and X is -O-. In some embodiments, "m" is 1 thus forming an ester group. In some embodiments, "m" is 0 and Z is H thus forming a carboxylic acid group.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is $-CH_2C(O)-$ or $-C(O)CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is –CHFC(O)- or –C(O)CHF-. In some embodiments W is $-CH(CH_3)C(O)-$ or $-C(O)CH(CH_3)-$ optionally substituted with halogen,

hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-C(OH)(CH_3)C(O)-$ or $-C(O)C(OH)(CH_3)$. In some embodiments W is $-C(CH_3)_2C(O)-$ or $-C(O)C(CH_3)_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**It**) and (**Iu**) respectively as illustrated below:

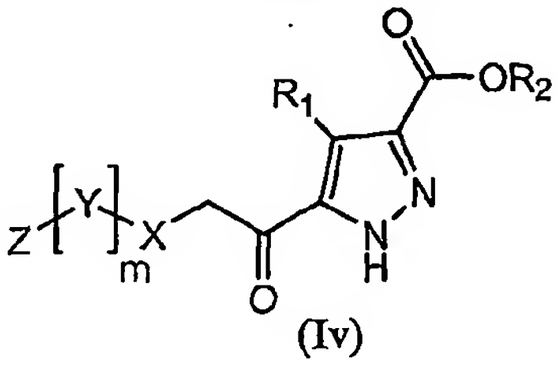


(**It**)

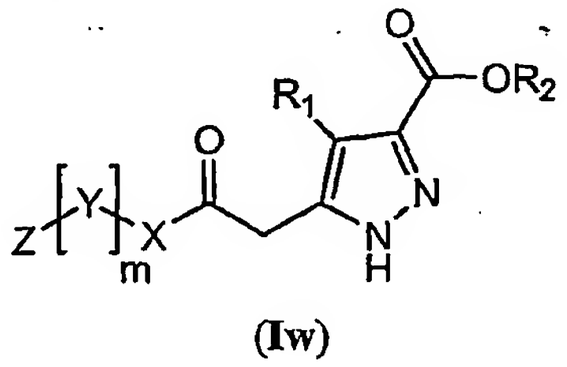


(**Iu**)

wherein each variable in Formulae (**It**) and (**Iu**) has the same meaning as described herein, *supra* and *infra*. Some embodiments of the present invention pertain to compounds of Formula (**It**) when X is -O- or $-NR_3-$. Some embodiments of the present invention include compounds of Formula (**Iu**) when X is -O-. In some embodiments W is $-CH_2C(O)-$ or $-C(O)CH_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**Iv**) and (**Iw**) respectively as illustrated below:



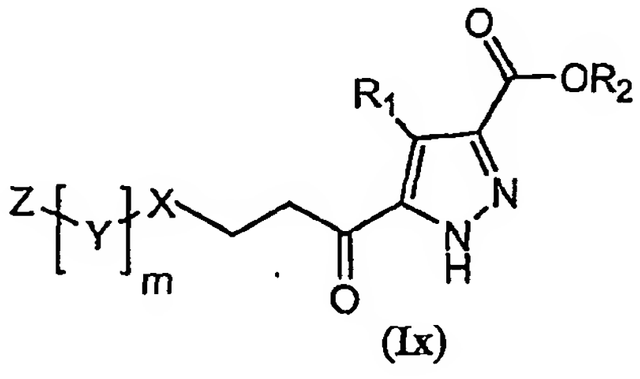
(**Iv**)



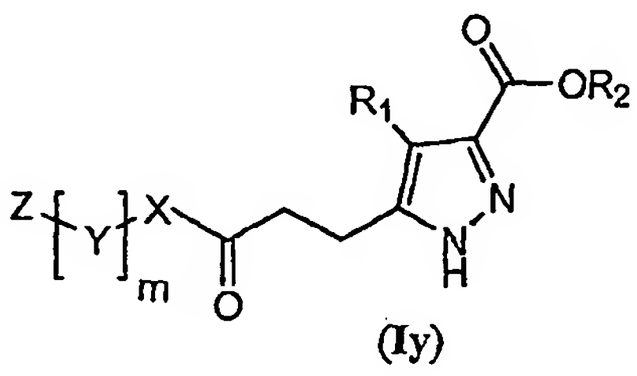
(**Iw**)

wherein each variable in Formulae (**Iv**) and (**Iw**) has the same meaning as described herein, *supra* and *infra*. Some embodiments of the present invention pertain to compounds of Formula (**Iv**) wherein X is -O- or $-NR_3-$. Some embodiments of the present invention pertain to compounds of Formula (**Iw**) when X is -O-.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is $-CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-C(CH_3)_2CH_2C(O)-$ or $-C(O)CH_2C(CH_3)_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is $-CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**Ix**) and (**Iy**) respectively as illustrated below:



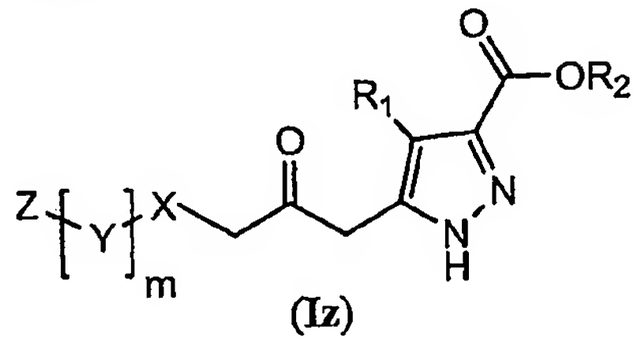
(**Ix**)



(**Iy**)

wherein each variable in Formulae (**Ix**) and (**Iy**) has the same meaning as described herein, *supra* and *infra*. Some embodiments of the present invention pertain to compounds of Formula (**Ix**) when X is -O- or -NR_3- and in still other embodiments R_3 is H or CH_3. Some embodiments of the present invention pertain to compounds of Formula (**Iy**) when X is -O-.

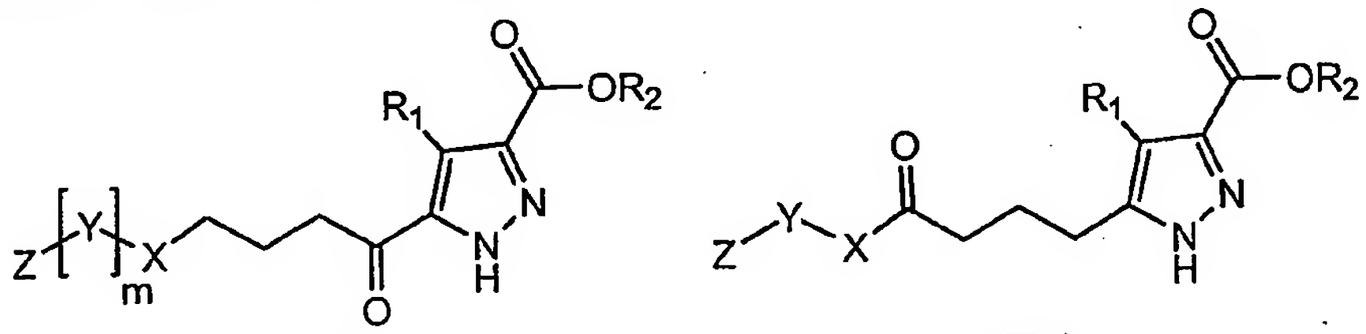
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -$CH_2C(O)CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is -$CH_2C(O)CH_2$-. In some embodiments, compounds of the present invention can be represented by Formula (**Iz**) as illustrated below:



(**Iz**)

wherein each variable in Formulae (**Iz**) has the same meaning as described herein, *supra* and *infra*.

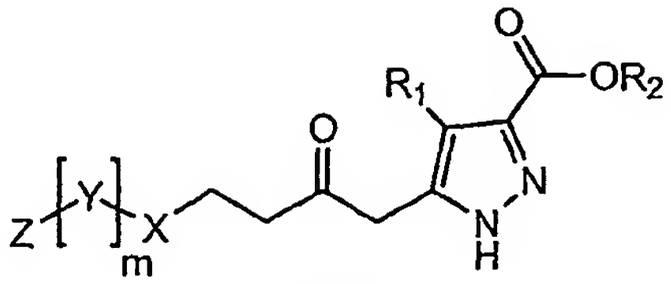
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -$CH_2CH_2CH_2C(O)$- or -$C(O)CH_2CH_2CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is -$CH(CH_3)CH_2CH_2C(O)$- or -$C(O)CH_2CH_2CH(CH_3)$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is -$CH_2CH_2CH_2C(O)$- or -$C(O)CH_2CH_2CH_2$-. In some embodiments, compounds of the present invention can be represented by Formulae (**IIa**) and (**IIb**) respectively as illustrated below:



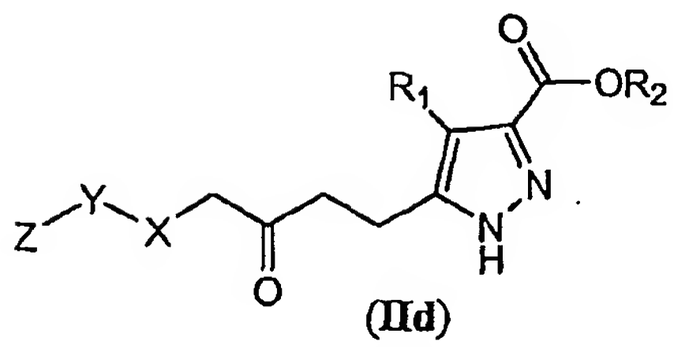
(**IIa**) (**IIb**)

wherein each variable in Formulae (**IIa**) and (**IIb**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -$CH_2CH_2C(O)CH_2$- or -$CH_2C(O)CH_2CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is -$CH_2CH_2C(O)CH_2$- or -$CH_2C(O)CH_2CH_2$-. In some embodiments, compounds of the present invention can be represented by Formulae (**IIc**) and (**IId**) respectively as illustrated below:



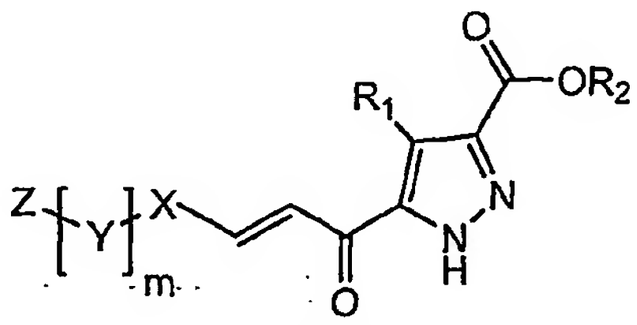
(IIc)



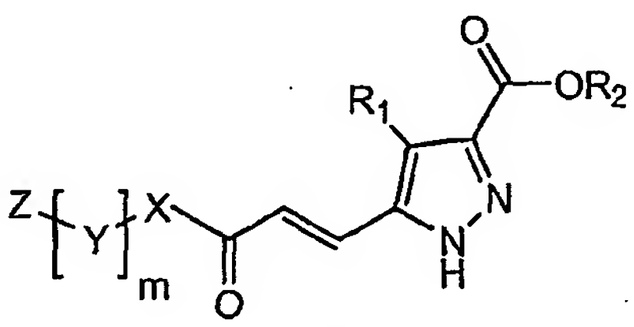
(IId)

wherein each variable in Formulae (**IIc**) and (**IId**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -CH=CHC(O)- or -C(O)CH=CH- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments W is -CH=CHC(O)- or -C(O)CH=CH-. In some embodiments, compounds of the present invention can be represented by Formulae (**IIe**) or (**IIf**) respectively as illustrated below:



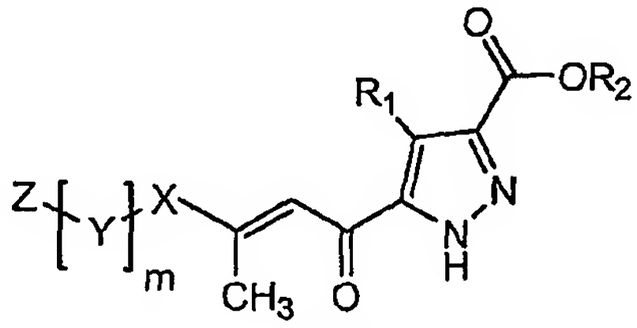
(IIe)



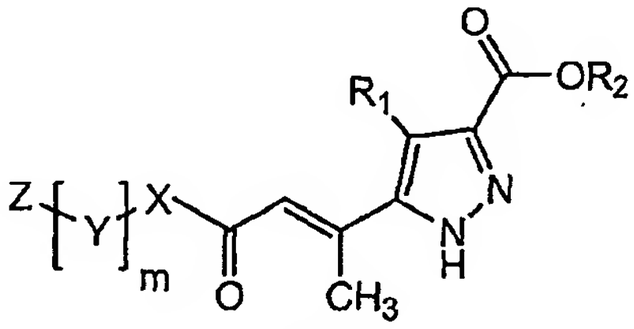
(IIf)

wherein each variable in Formulae (**IIe**) and (**IIf**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein W is -C(CH_3)=CHC(O)- or -C(O)CH=C(CH_3)- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In one embodiment, W is -C(CH_3)=CHC(O)- or -C(O)CH=C(CH_3)-. In some embodiments, compounds of the present invention can be represented by either Formulae (**IIg**) or (**IIh**) respectively as illustrated below:



(IIg)



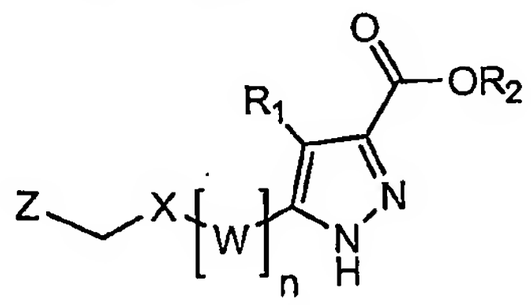
(IIh)

wherein each variable in Formulae (**IIg**) and (**IIh**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is the C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. The C_{1-5} alkylene group is a straight chain group of 1 to 5 carbons. In some embodiments the alkylene chain consists of single bonds. In some embodiments two

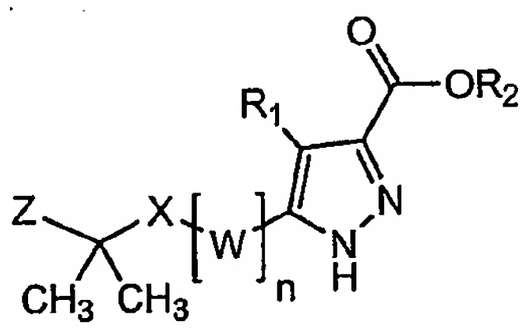
adjacent carbons in this chain can be bonded together by a double bond or a triple bond, in still other embodiments, a single carbon can be bonded to an oxygen by a double bond thus forming a carbonyl group as represented in some embodiments disclosed herein, can be depicted as -C(=O)-.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein Y is $-CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (IIi) as illustrated below:



(IIi)

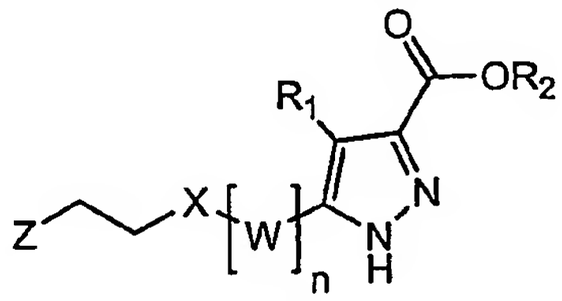
wherein each variable in Formula (IIi) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is $-CH(CH_3)-$ optionally substituted with halogen, hydroxyl or C_{1-4} alkoxy. In some embodiments Y is $-C(CH_3)_2-$. In some embodiments, compounds of the present invention can be represented by Formula (IIj) as illustrated below:



(IIj)

wherein each variable in Formula (IIj) has the same meaning as described herein, *supra* and *infra*.

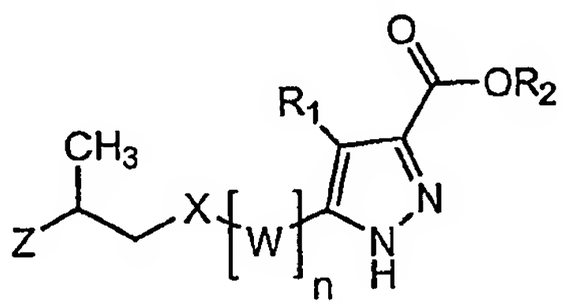
Some embodiments of the present invention pertain to compounds of Formula (I) wherein Y is $-CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (IIk) as illustrated below:



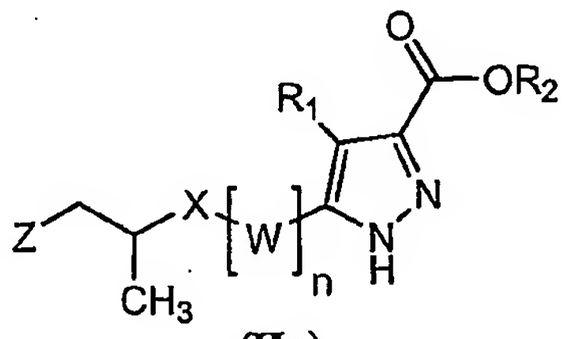
(IIk)

wherein each variable in Formula (IIk) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH(CH_3)CH_2-$

or -$CH_2CH(CH_3)$-. In some embodiments, compounds of the present invention can be represented by Formulae (**IIm**) and (**IIn**) respectively as illustrated below:

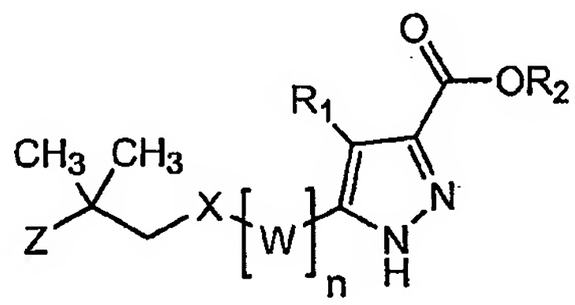


(**IIm**)

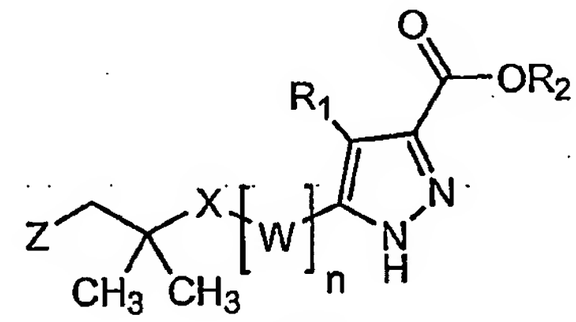


(**IIn**)

wherein each variable in Formulae (**IIm**) and (**IIn**) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is -$C(CH_3)_2CH_2$- or -$CH_2C(CH_3)_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $C(CH_3)_2CH_2$- or -$CH_2C(CH_3)_2$-. In some embodiments, compounds of the present invention can be represented by Formulae (**IIo**) and (**IIp**) respectively as illustrated below:

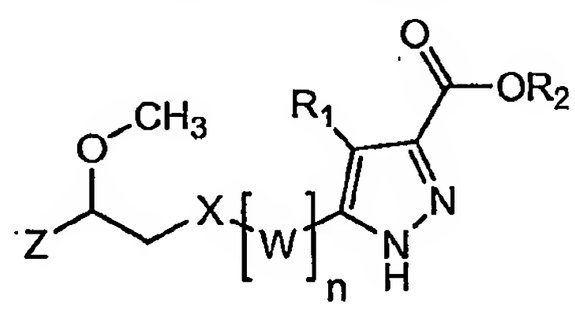


(**IIo**)

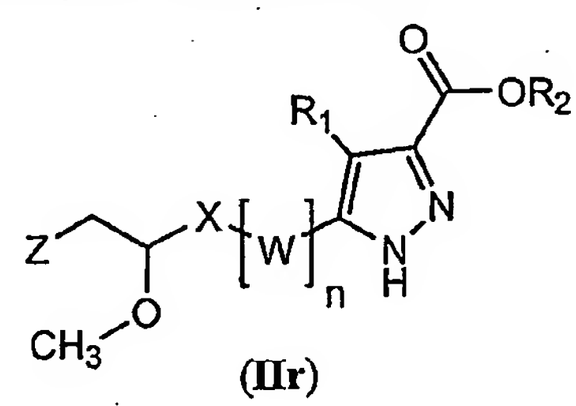


(**IIp**)

wherein each variable in Formulae (**IIo**) and (**IIp**) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is -$CH(OCH_3)CH_2$- or -$CH_2CH(OCH_3)$- optionally substituted with halogen, hydroxyl or C_{1-4} alkyl. In some embodiments Y is -$CH(OCH_3)CH_2$- or -$CH_2CH(OCH_3)$-. In some embodiments, compounds of the present invention can be represented by Formulae (**IIq**) and (**IIr**) respectively as illustrated below:



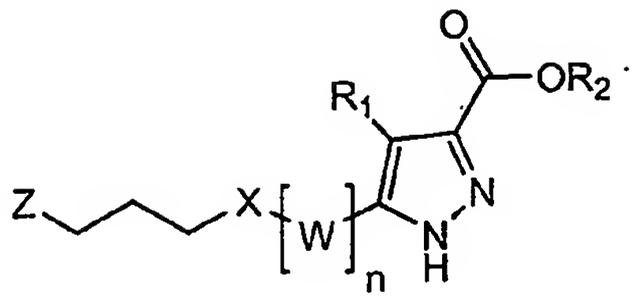
(**IIq**)



(**IIr**)

wherein each variable in Formulae (**IIq**) and (**IIr**) has the same meaning as described herein, *supra* and *infra*.

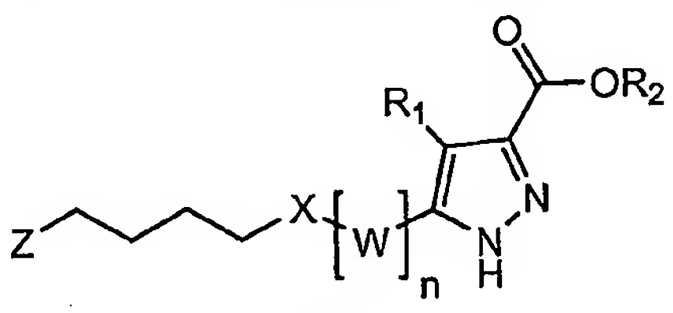
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is -$CH_2CH_2CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is -$CH_2CH_2CH_2$-. In some embodiments, compounds of the present invention can be represented by Formula (**IIs**) as illustrated below:



(IIs)

wherein each variable in Formula (**IIs**) has the same meaning as described herein, *supra* and *infra*.

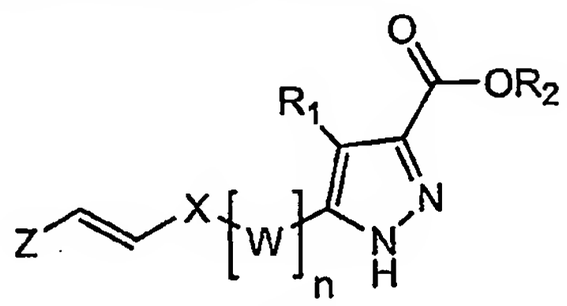
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-CH_2CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH_2CH_2CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**IIt**) as illustrated below:



(IIt)

wherein each variable in Formula (**IIt**) has the same meaning as described herein, *supra* and *infra*.

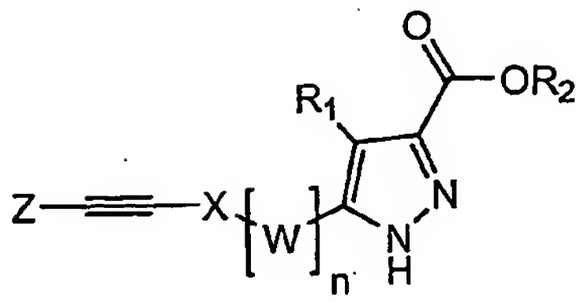
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is -CH=CH- optionally substituted with C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is -CH=CH-. In some embodiments, compounds of the present invention can be represented by Formula (**IIu**) as illustrated below:



(IIu)

wherein each variable in Formula (**IIu**) has the same meaning as described herein, *supra* and *infra*.

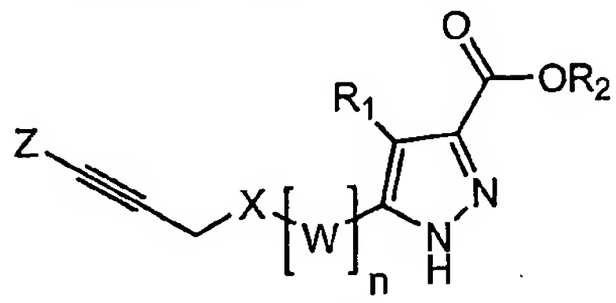
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-C\equiv C-$. In some embodiments, compounds of the present invention can be represented by Formula (**IIv**) as illustrated below:



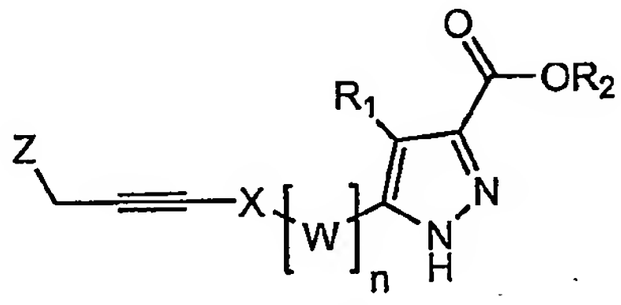
(IIv)

wherein each variable in Formula (IIv) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein Y is $-C\equiv CCH_2-$ or $-CH_2C\equiv C-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-C\equiv CCH_2-$ or $-CH_2C\equiv C-$. In some embodiments, compounds of the present invention can be represented by Formulae (IIw) and (IIx) respectively as illustrated below:



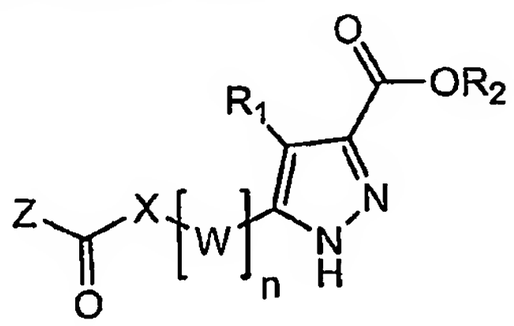
(IIw)



(IIx)

wherein each variable in Formulae (IIw) and (IIx) has the same meaning as described herein, *supra* and *infra*.

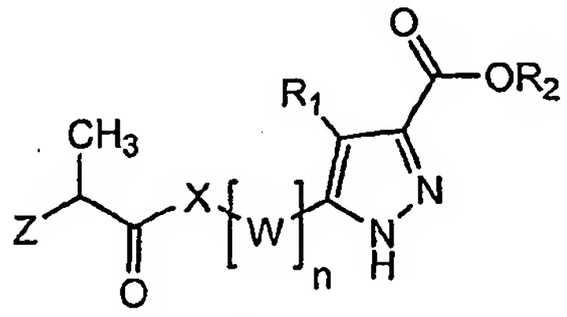
Some embodiments of the present invention pertain to compounds of Formula (I) wherein Y is -C(O)-. In some embodiments, compounds of the present invention can be represented by Formula (IIy) as illustrated below:



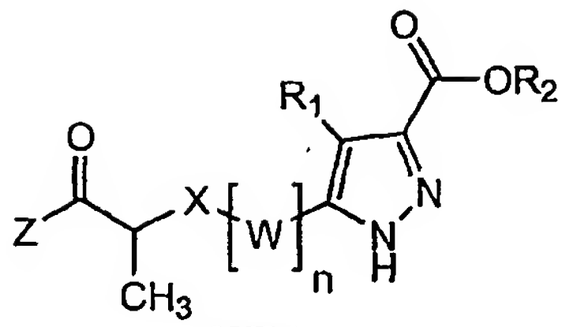
(IIy)

wherein each variable in Formula (IIy) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein Y is $-CH_2C(O)-$ or $-C(O)CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH(CH_3)C(O)-$ or $-C(O)CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH(CH_3)C(O)-$ or $-C(O)CH(CH_3)-$. In some embodiments, compounds of the present invention can be represented by Formulae (IIIa) and (IIIb) respectively as illustrated below:

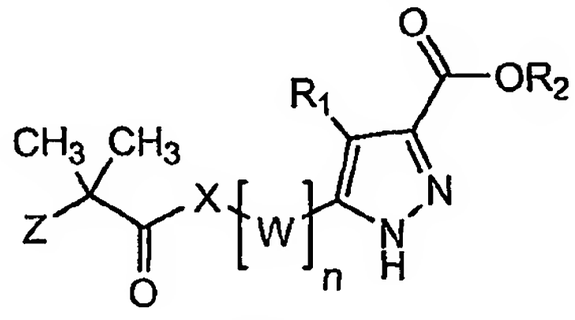


(IIIa)

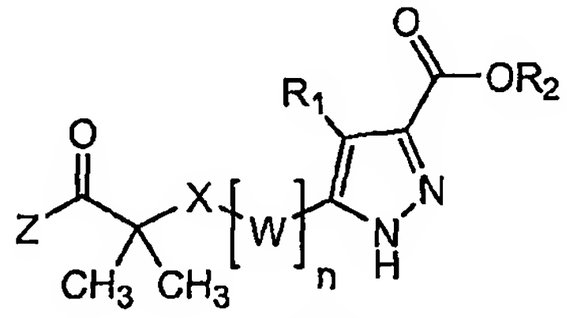


(IIIb)

wherein each variable in Formulae (**IIIa**) and (**IIIb**) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is $-C(CH_3)_2C(O)-$ or $-C(O)C(CH_3)_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIc**) and (**IIId**) respectively as illustrated below:

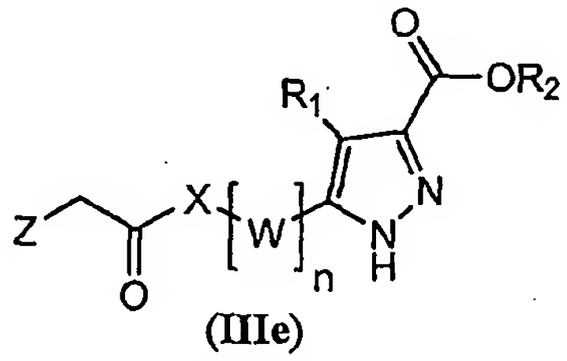


(IIIc)

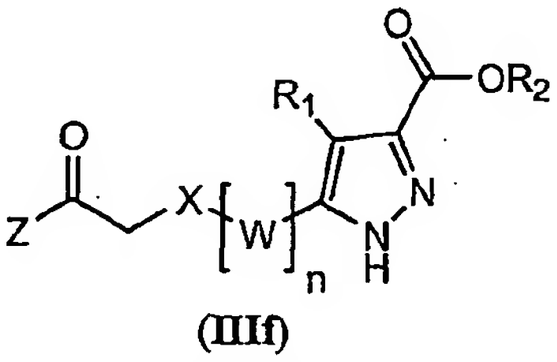


(IIId)

wherein each variable in Formulae (**IIIc**) and (**IIId**) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is $-CH_2C(O)-$ or $-C(O)CH_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIe**) and (**IIIf**) respectively as illustrated below:



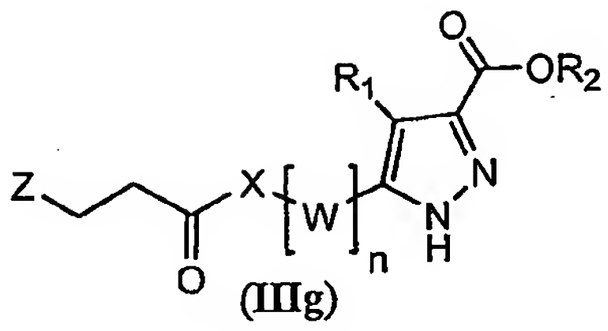
(IIIe)



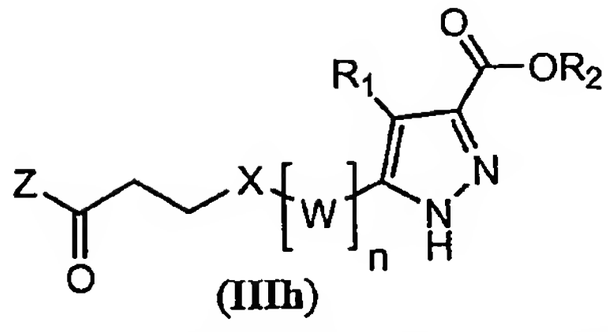
(IIIf)

wherein each variable in Formulae (**IIIe**) and (**IIIf**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-C(CH_3)_2CH_2C(O)-$ or $-C(O)CH_2C(CH_3)_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIg**) and (**IIIh**) respectively as illustrated below:



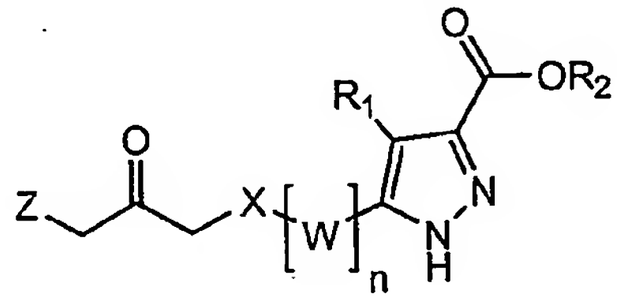
(IIIg)



(IIIh)

wherein each variable in Formulae (**IIIg**) and (**IIIh**) has the same meaning as described herein, *supra* and *infra*.

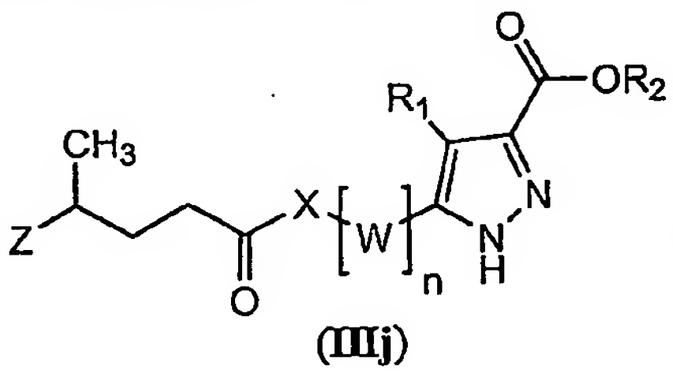
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-CH_2C(O)CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH_2C(O)CH_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**IIIi**) as illustrated below:



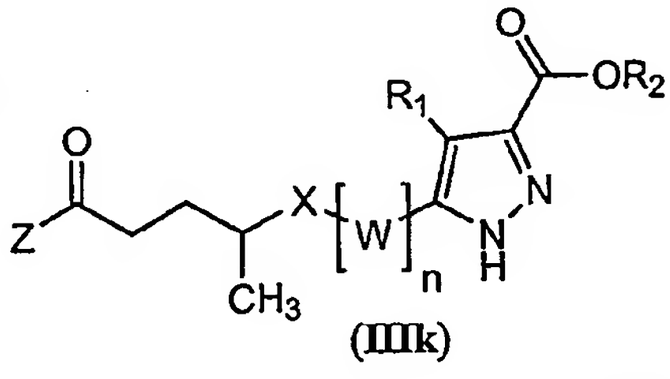
(IIIi)

wherein each variable in Formula (**IIIi**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-CH_2CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH(CH_3)CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH(CH_3)CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2CH(CH_3)-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIj**) and (**IIIk**) respectively as illustrated below:

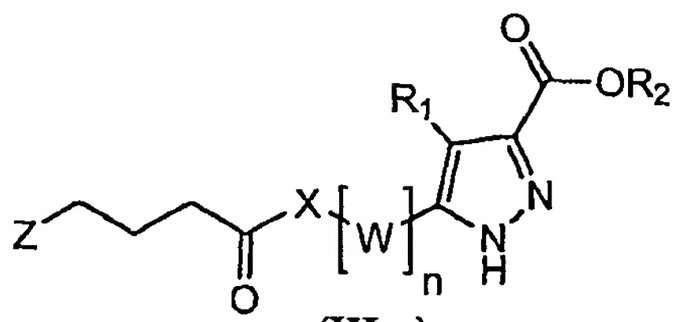


(IIIj)

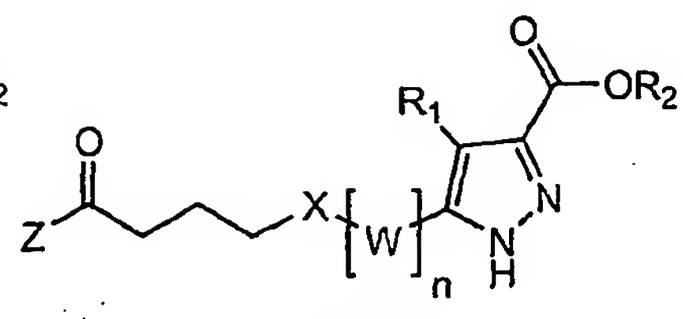


(IIIk)

wherein each variable in Formulae (**IIIj**) and (**IIIk**) has the same meaning as described herein, *supra* and *infra*. In some embodiments Y is $-CH_2CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIm**) and (**IIIn**) respectively as illustrated below:



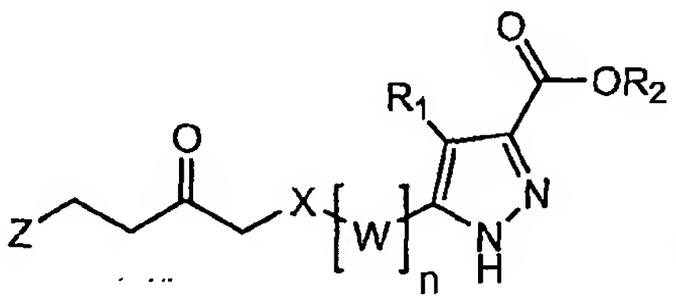
(IIIm)



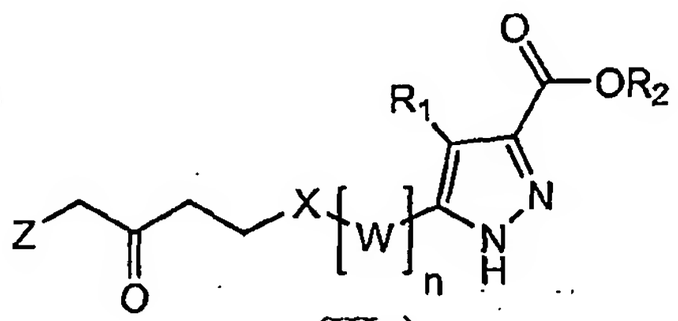
(IIIn)

wherein each variable in Formulae (**IIIm**) and (**IIn**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-CH_2CH_2C(O)CH_2-$ or $-CH_2C(O)CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH_2CH_2C(O)CH_2-$ or $-CH_2C(O)CH_2CH_2-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIo**) and (**IIIp**) respectively as illustrated below:



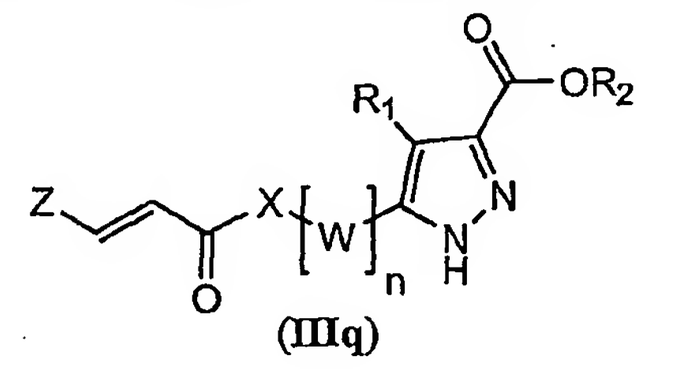
(IIIo)



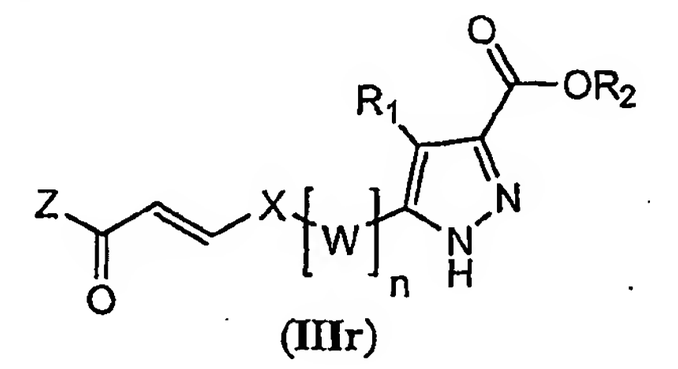
(IIIp)

wherein each variable in Formulae (**IIIo**) and (**IIIp**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-CH=CHC(O)-$ or $-C(O)CH=CH-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-CH=CHC(O)-$ or $-C(O)CH=CH-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIq**) and (**IIIr**) respectively as illustrated below:



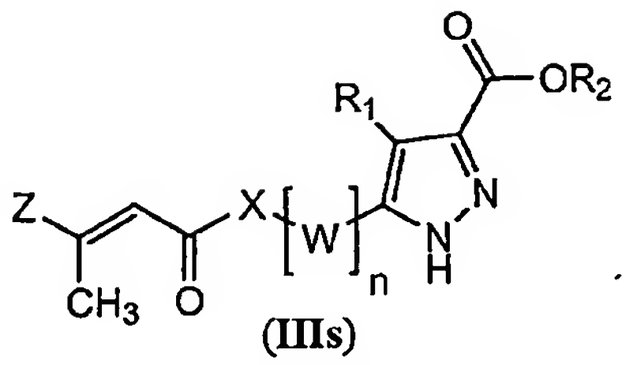
(IIIq)



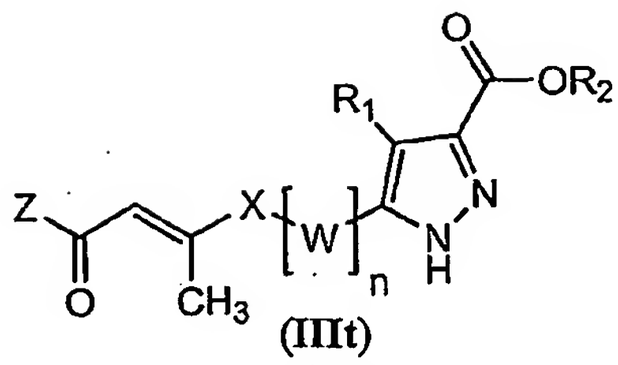
(IIIr)

wherein each variable in Formulae (**IIIq**) and (**IIIr**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Y is $-C(CH_3)=CHC(O)-$ or $-C(O)CH=C(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy. In some embodiments Y is $-C(CH_3)=CHC(O)-$ or $-C(O)CH=C(CH_3)-$. In some embodiments, compounds of the present invention can be represented by Formulae (**IIIs**) and (**IIIt**) respectively as illustrated below:



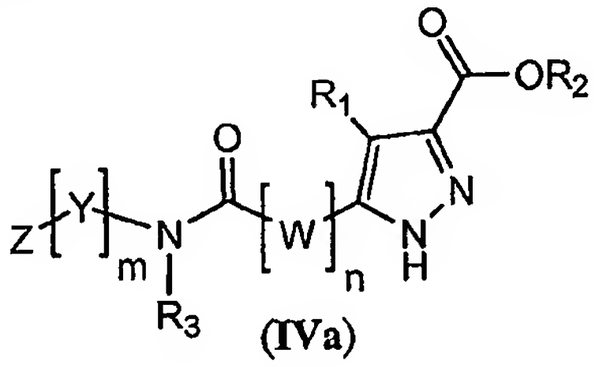
(IIIs)



(IIIt)

wherein each variable in Formulae **(IIIs)** and **(IIIt)** has the same meaning as described herein, *supra* and *infra*.

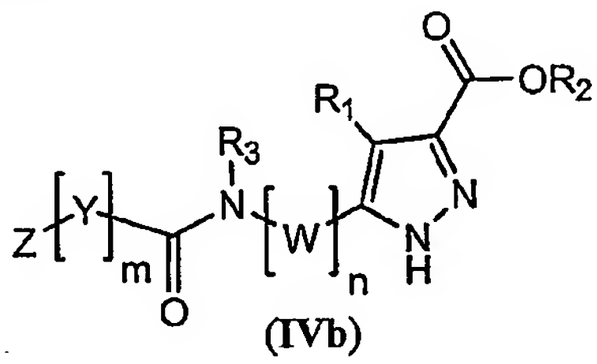
Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein X is $-NR_3C(O)-$. In some embodiments, compounds of the present invention can be represented by Formula **(IVa)** as illustrated below:



(IVa)

wherein each variable in Formula **(IVa)** has the same meaning as described herein, *supra* and *infra*.

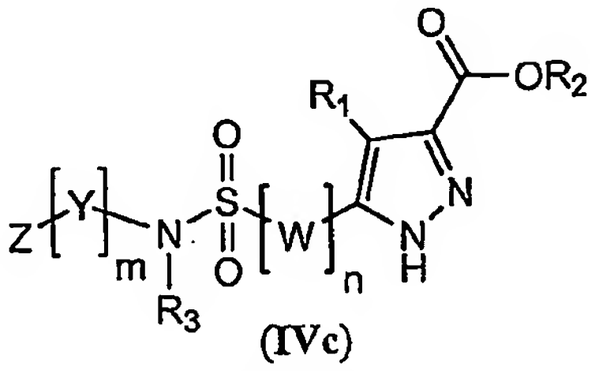
Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein X is $-C(O)NR_3-$. In some embodiments, compounds of the present invention can be represented by Formula **(IVb)** as illustrated below:



(IVb)

wherein each variable in Formula **(IVb)** has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein X is $-NR_3S(O)_2-$. In some embodiments, compounds of the present invention can be represented by Formula **(IVc)** as illustrated below:

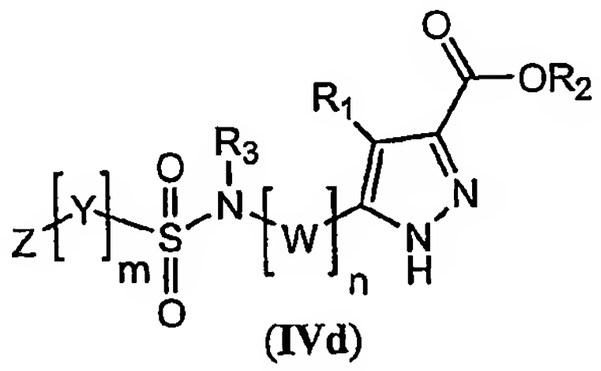


(IVc)

wherein each variable in Formula **(IVc)** has the same meaning as described herein, *supra* and

infra.

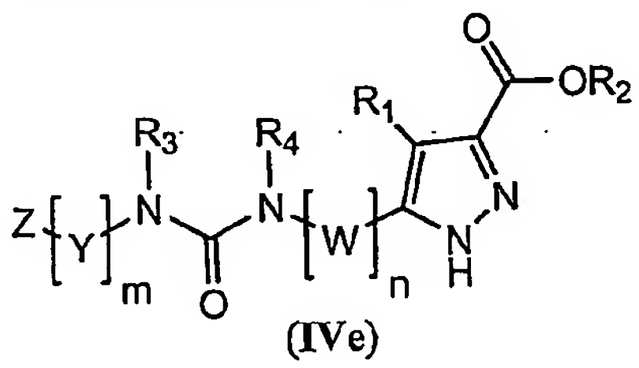
Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is $-S(O)_2NR_3-$. In some embodiments, compounds of the present invention can be represented by Formula (IVd) as illustrated below:



(IVd)

wherein each variable in Formula (IVd) has the same meaning as described herein, *supra* and *infra*.

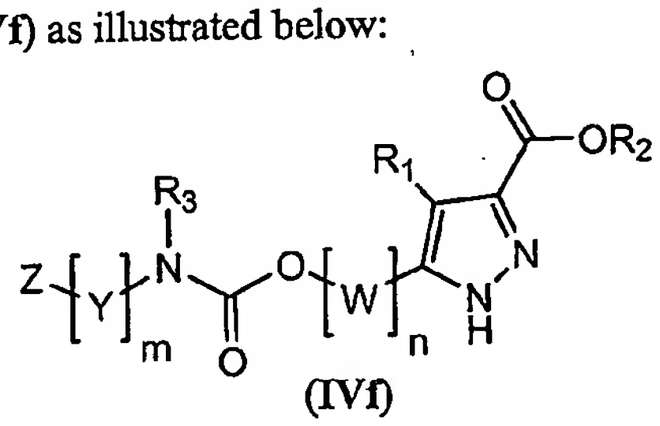
Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is $-NR_3C(O)NR_4-$. In some embodiments, compounds of the present invention can be represented by Formula (IVe) as illustrated below:



(IVe)

wherein each variable in Formula (IVe) has the same meaning as described herein, *supra* and *infra*.

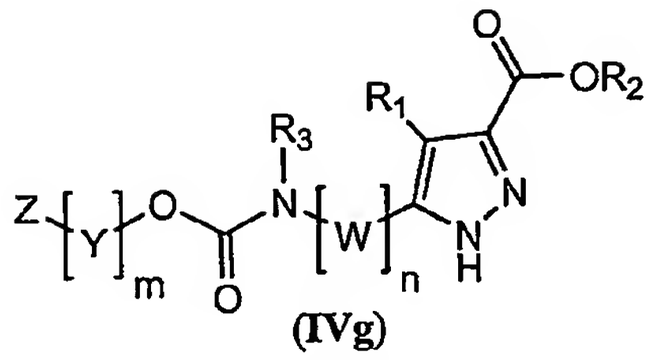
Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is $-NR_3C(O)O-$. In some embodiments, compounds of the present invention can be represented by Formula (IVf) as illustrated below:



(IVf)

wherein each variable in Formula (IVf) has the same meaning as described herein, *supra* and *infra*.

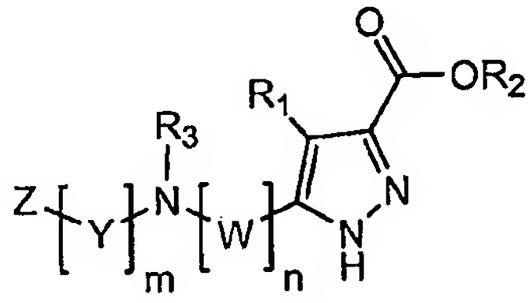
Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is $-OC(O)NR_3-$. In some embodiments, compounds of the present invention can be represented by Formula (IVg) as illustrated below:



(IVg)

wherein each variable in Formula **(IVg)** has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein X is $-NR_3-$. In some embodiments, compounds of the present invention can be represented by Formula **(IVh)** as illustrated below:



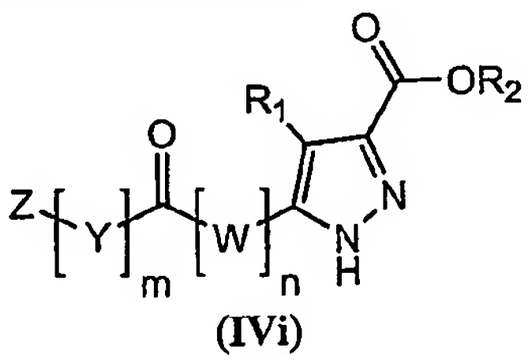
(IVh)

wherein each variable in Formula **(IVh)** has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein R_3 is H or CH_3.

Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein R_4 is H or CH_3.

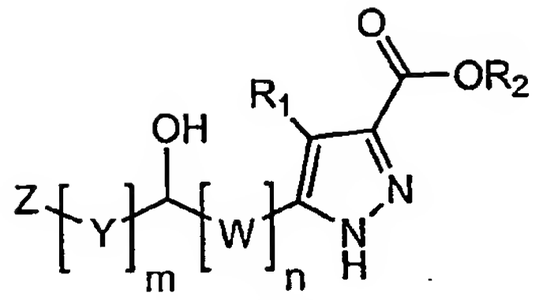
Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein X is -C(O)-. In some embodiments, compounds of the present invention can be represented by Formula **(IVi)** as illustrated below:



(IVi)

wherein each variable in Formula **(IVi)** has the same meaning as described herein, *supra* and *infra*.

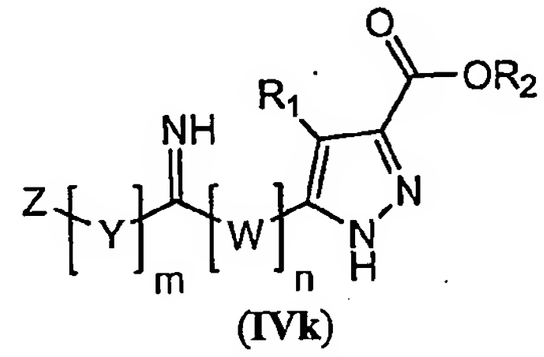
Some embodiments of the present invention pertain to compounds of Formula **(I)** wherein X is -CH(OH)-. In some embodiments, compounds of the present invention can be represented by Formula **(IVj)** as illustrated below:



(IVj)

wherein each variable in Formula (IVj) has the same meaning as described herein, *supra* and *infra*.

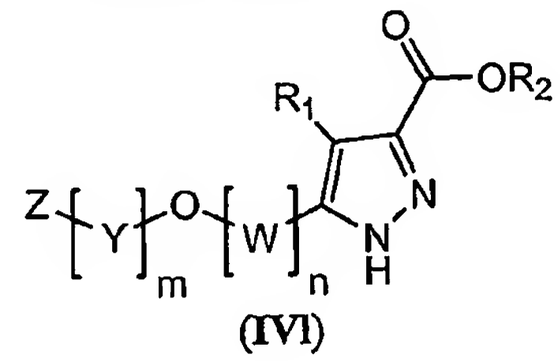
Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is -C(NH)-. In some embodiments, compounds of the present invention can be represented by Formula (IVk) as illustrated below:



(IVk)

wherein each variable in Formula (IVk) has the same meaning as described herein, *supra* and *infra*.

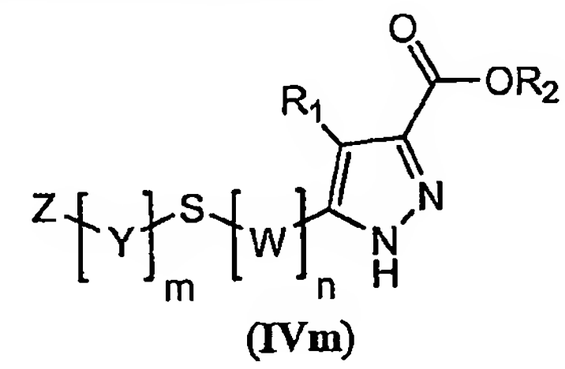
Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is -O-. In some embodiments, compounds of the present invention can be represented by Formula (IVl) as illustrated below:



(IVl)

wherein each variable in Formula (IVl) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein X is -S-. In some embodiments, compounds of the present invention can be represented by Formula (IVm) as illustrated below:

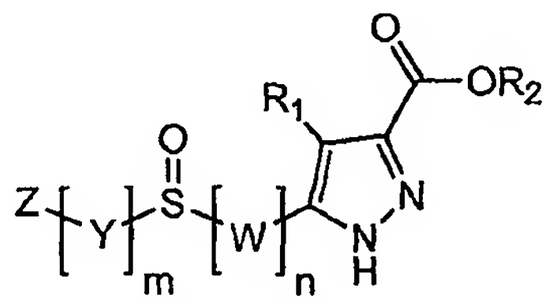


(IVm)

wherein each variable in Formula (IVm) has the same meaning as described herein, *supra* and

infra.

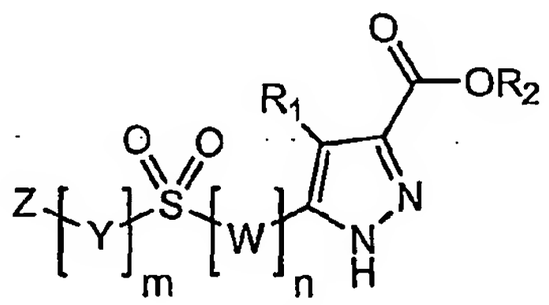
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein X is -S(O)-. In some embodiments, compounds of the present invention can be represented by Formula (**IVn**) as illustrated below:



(IVn)

wherein each variable in Formula (**IVn**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein X is $-S(O)_2-$. In some embodiments, compounds of the present invention can be represented by Formula (**IVo**) as illustrated below:



(IVo)

wherein each variable in Formula (**IVo**) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Z is H.

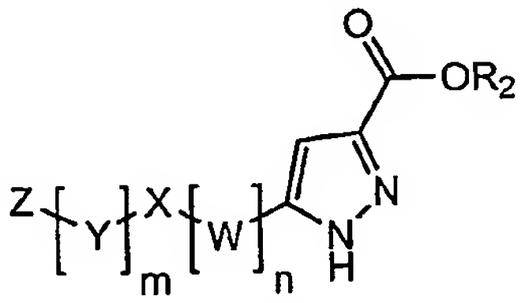
Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Z is halogen.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Z is phenyl. In some embodiments the phenyl is optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, C_{1-4} haloalkyl, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl. In some embodiments the phenyl is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, $-CF_3$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$ and $-OCF_3$.

Some embodiments of the present invention pertain to compounds of Formula (**I**) wherein Z is heteroaryl. In some embodiments the heteroaryl is optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, C_{1-4} haloalkyl, C_{1-4}

alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl. In some embodiments the phenyl is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, $-CF_3$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$ and $-OCF_3$.

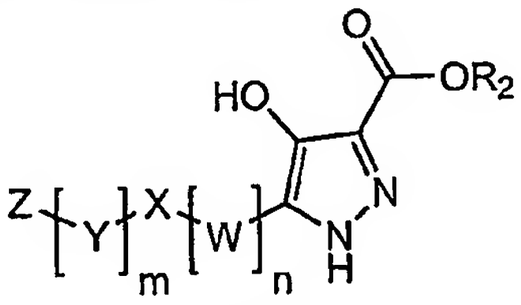
Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_1 is H. In some embodiments, compounds of the present invention can be represented by Formula (IVp) as illustrated below:



(IVp)

wherein each variable in Formula (IVp) has the same meaning as described herein, *supra* and *infra*.

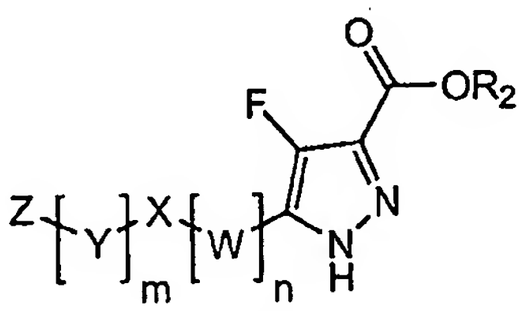
Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_1 is hydroxyl. In some embodiments, compounds of the present invention can be represented by Formula (IVq) as illustrated below:



(IVq)

wherein each variable in Formula (IVq) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_1 is halogen. In some embodiments R_1 is F, Cl or Br. In still further embodiments, R_1 is F (a fluorine atom). In some embodiments, compounds of the present invention can be represented by Formula (IVr) as illustrated below:



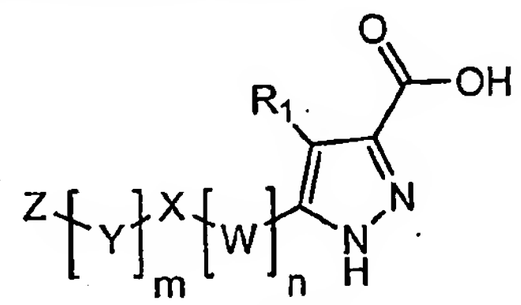
(IVr)

wherein each variable in Formula (IVr) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_1 is C_{1-4} alkyl.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_1 is C_{1-4} haloalkyl.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_2 is H. In some embodiments, compounds of the present invention can be represented by Formula (IVs) as illustrated below:



(IVs)

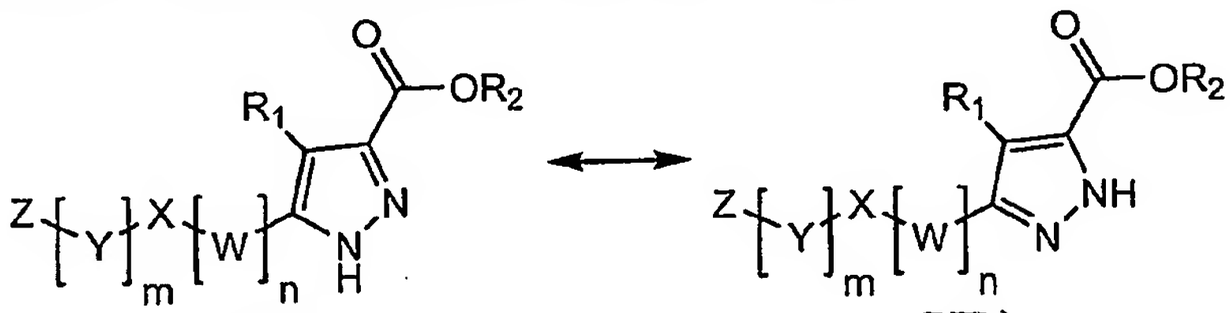
wherein each variable in Formula (IVs) has the same meaning as described herein, *supra* and *infra*.

Some embodiments of the present invention pertain to compounds of Formula (I) wherein R_2 is C_{1-8} alkyl.

CHEMISTRY OF THE PRESENT INVENTION

Tautomers

Although compounds of the present invention of Formula (I) are depicted as one compound, it is well understood and appreciated in the art that pyrazoles can exist in various tautomeric forms. Two possible tautomeric forms are illustrated below:



(VIa) (VIb)

Accordingly, tautomeric forms can have corresponding nomenclature, for example, Formula (VIa) and Formula (VIb) can be represented by the general chemical names 1*H*-pyrazole and 2*H*-pyrazole respectively. Therefore, for convenience, compounds presented herein by Formula (I) are understood to include all tautomers and furthermore, these tautomers and various nomenclature designations are within the scope of the present invention.

Enantiomers, Diastereomers and mixtures thereof:

Compounds of Formula (I) may have one or more chiral centers, and therefore exist as enantiomers or diastereomers. The invention is understood to extend to all such

enantiomers, diastereomers and mixtures thereof, including racemates. Formula (I) and the formulae described herein, *supra*, are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

Racemic mixtures can be resolved into the optical pure enatiomers by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical pure enatiomers is based upon chromatography on an optically active matrix or chiral support. Certain racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric amides or ester by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like subsequently hydrolyzed.

Additional methods for the resolution of optical isomers, known to those skilled in the art can be used, and will be apparent to the average worker skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

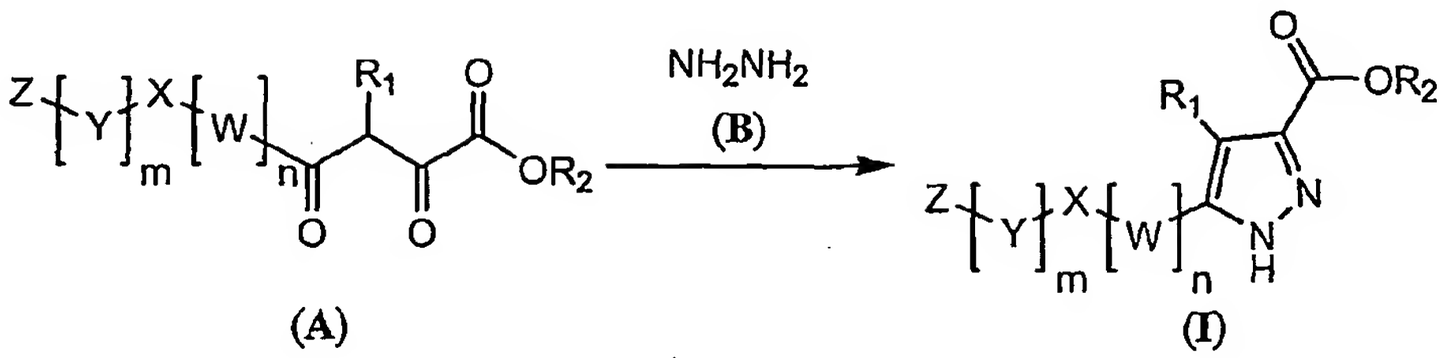
Synthesis of Compounds of Formula (I)

The compounds of the present invention can be readily prepared according to a variety of synthetic regimes, all of which would be familiar to one skilled in the art. The chemical and patent literature quotes numerous procedures for the synthesis of pyrazole carboxylic acids and esters. Some of these articles include: Ashton and co-workers, *J. Med. Chem.* **1993**, *36*, 3595-3605; Seki and co-workers, *Chem. Pharm. Bull.*, 1984, *32*, 1568; and Wiley and Hexner, *Org. Syn Coll IV*, **1963**, 351.

Also provided is a novel procedure for the preparation of novel pyrazoles of Formula (I).

In the illustrated syntheses outlined below, the labeled substituents have the same identifications as set out in the definitions of the compound described above for Formula (I). The methods described below can be used for the preparation of compounds of the invention.

One method that can be used to prepare compounds of Formula (I) utilizes intermediates of Formula (A) as illustrated in Reaction Scheme (1) below:



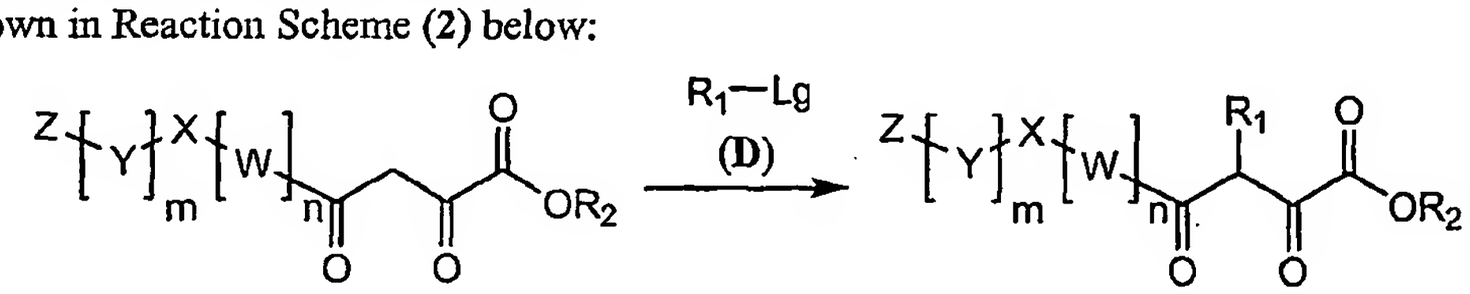
(A) (I)

Reaction Scheme (1)

Compounds of Formula (**I**) can be prepared by treating the 2,4-diketo ester or acid [R_2 = alkyl or H respectively, (**A**)] with hydrazine (**B**) under various conditions. For example, the solvent may optionally be present or absent. In the instance that the solvent is absent then the hydrazine (**B**) serves both as a reactant and as the solvent. Typically, under these conditions hydrazine would be present in molar excess. In the instance when the solvent is present, the solvent can be a polar solvent and is generally a C_1-C_6 alcohol. Some typical solvents can be selected from, but not limited to, the group consisting of methanol, ethanol, butanol, pentanol, hexanol, 2-methoxyethanol, 1-propanol and 2-propanol. In some instances it can be beneficial to include the presence of an acid. Some representative examples of acids that can be used can be selected from the group consisting of hydrochloric acid, hydrobromic acid, acetic acid and trifluoroacetic acid. The reaction temperature generally ranges from about 20°C to about 160°C, and for convenience, the reaction temperature is typically the reflux temperature of the reaction mixture.

The 2,4-diketo esters or acids (**A**) are commercially available or can be obtained by methods known in the art, Seki and co-workers, *Chem. Pharm. Bull.*, 1984, *32*, 1568. It is appreciated that a group on the Z-$[Y]_m$-X-$[W]_n$- chain of (**A**) can be protected by methods known in the art if such protection is required.

One particular feature of 2,4-diketo esters or acids (**A**) is that a diverse number of R_1 groups can be introduced by a variety of methods known in the art, such as, alkylation, as shown in Reaction Scheme (**2**) below:

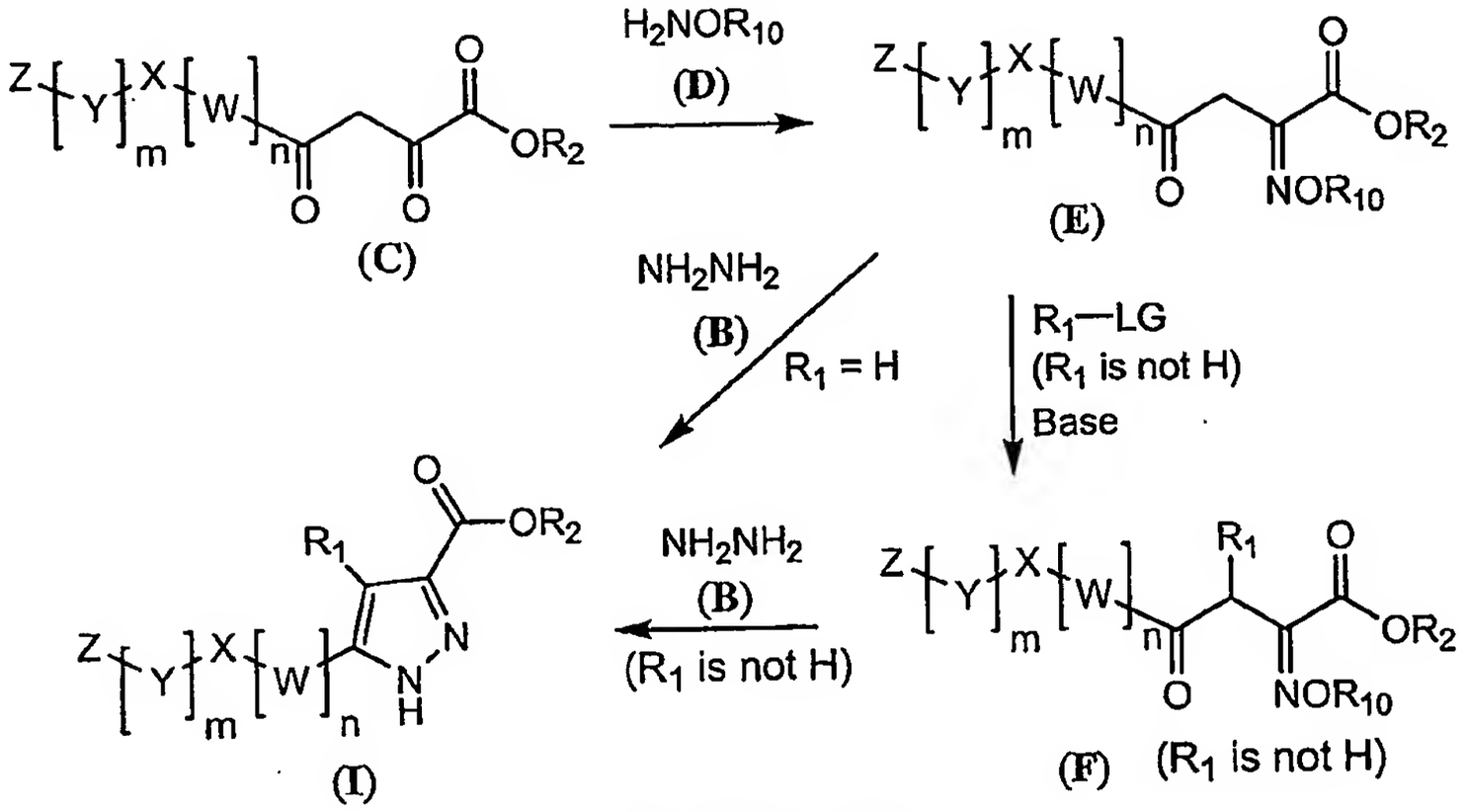


(C) (A) (In this example, R_1 is not H)

Reaction Scheme (2)

The alkylation step as shown in Reaction Scheme (**2**) is similar to and in some instances identical to that described in the preparation of intermediate (**F**), *infra*.

Utilizing a similar starting material as in Reaction Scheme (**1**) an alternative method can be used to prepare compounds of Formula (**I**) as illustrated in Reaction Scheme (**3**) below:

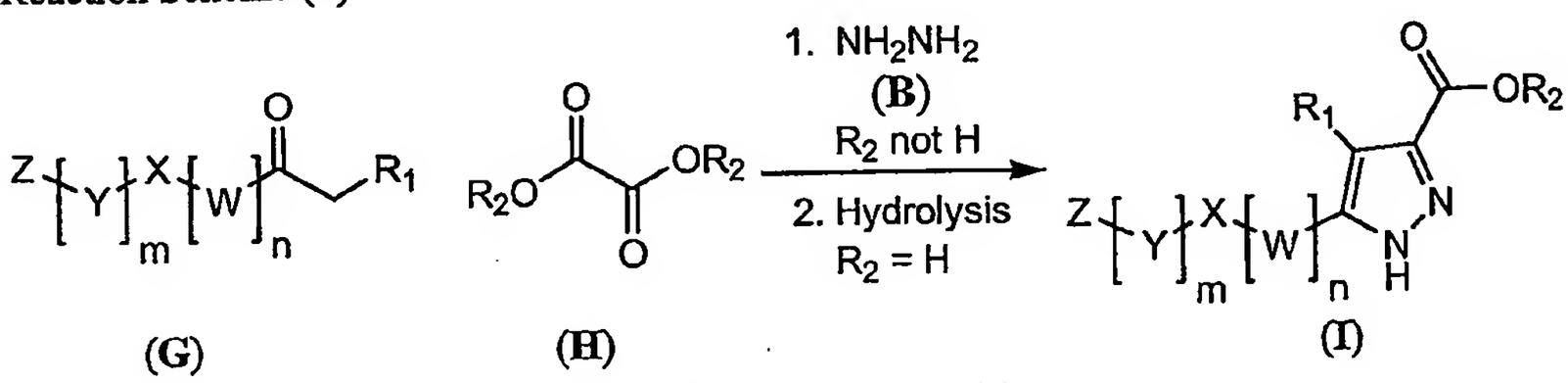


Reaction Scheme (3)

Compounds of Formula (**I**) can be prepared by treating 2,4-diketo ester or acid (**C**), preferably the ester, with an alkoxyamine of Formula (**D**) where R_{10} is C_1-C_8 alkyl, leading to 2-(methoxyimino) intermediate of Formula (**E**). Typically, the alkoxyamine is methoxyamine (i.e., O-methyl hydroxylamine) wherein R_{10} is methyl. This step is typically conducted in the presence of a drying agent to concomitantly remove the water formed during the process; examples of a drying agent that can be used include molecular sieves, magnesium sulfate and the like. In the subsequent step, the intermediate of Formula (**E**) can be functionalized with R_1 utilizing methods known in the art. One example may use R_1-LG, wherein LG is a leaving group, such as, iodo, bromo, mesylate and the like, in the presence of a base and a polar solvent. Typical bases can be selected from, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, LDA, sodium methoxide, sodium ethoxide and the like; and the polar solvent can be dimethylformamide, dimethylsulfoxide, THF and the like. It is understood that this step is optional since in some embodiments of the invention R_1 is H. In this context, as depicted in Reaction Scheme (3), intermediate (**E**) can be converted to a compound of Formula (**I**) wherein R_2 is H using hydrazine (**B**). This step can be performed under heating conditions in an alcoholic solvent as described above in Reaction Scheme (**1**). Optionally, an acid can be present, such as HCl. Similarly, in the example where R_1 is not H, intermediate (**F**) can be treated with hydrazine (**B**) in a manner as described above to provide compounds of Formula (**I**) where R_1 is a group other than H.

It is understood that in reference to Reaction Scheme (3), a compound of Formula (**C**) can be functionalized with R_1 as described above prior to treating with alkoxyamine (**D**) to give the same intermediate (**F**). Absent any chemical reason that would be known in the art, the order of the steps can be changed and can be more a matter of convenience than necessity [i.e., (**C**) to (**E**) to (**F**); or (**C**) to (**A**) to (**F**)].

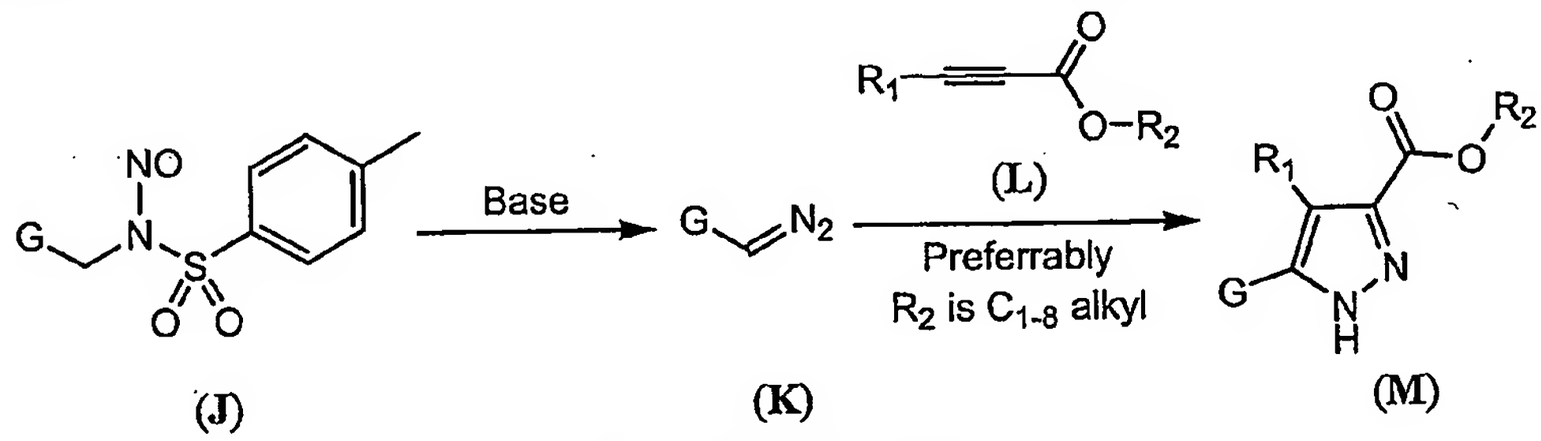
A novel method for the preparation of compounds of Formula (I) is shown in Reaction Scheme (4).



Reaction Scheme (4)

In this procedure, ketone (G) is allowed to react with a base, such as sodium methoxide or other alkali metal alkoxide, in the presence of oxalate (H). The resulting mixture is treated with hydrazine (B) to compounds of the present invention wherein R_2 is alkyl. As an optional step, the ester can be converted to the carboxylic acid by methods known in the art.

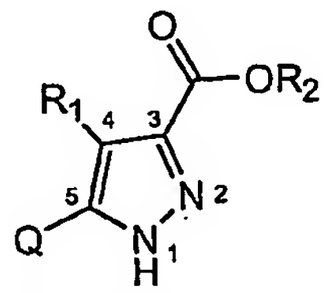
Another method for the preparation of compounds of Formula (I) is set forth in Reaction Scheme (5) and is intended to be illustrative and not limited.



Reaction Scheme (5)

Compounds of Formula (I) can be prepared by treating a nitroso sulfonamide (L) with base to give a substituted diazoalkane (K). A wide variety of functionality can be present in this synthesis, for example, G can be $(CH_3O)_2CH$- as shown in Example *infra*. Once formed, the substituted diazoalkane (K) can undergo a cycloaddition process with alkyne (L) to give pyrazole (M). A variety of alkynes can be either prepared or purchased from commercial sources to introduce the R_1 group as defined herein. Preferrably, R_1 in Reaction Scheme (5) is H, C_{1-4} alkyl or C_{1-4} haloalkyl.

It is understood that various pyrazoles can be prepared with groups present at the 5-position and these groups can be further converted or modified using methods known in the art into compounds of Formula (I).



For example, Q can be a group represented by formula H_2N-$[W]_n$-, wherein "W" and "n" have the same meaning as used herein. The amine group can be modified with a variety

of substituted aldehydes or ketones, such as those commercially available or prepared by methods known in the art, through a reductive amination procedure or similar method. Further, the amine can also be alkylated with Z-$[Y]_m$-Lg wherein Lg is a leaving group as defined herein, *supra*. In addition, the amine can also be modified with a variety of electrophils, such as Z-$[Y]_m$-C(O)-Lg (i.e., an acid halide or anhydride), Z-$[Y]_m$-$S(O)_2$-Lg (i.e., a sulfonyl halide) or Z-$[Y]_m$-N=C=O. In the examples where R_3 is not H, the amine can be further substituted with the R_3 group via methods known in the art. In another example, Q can be HX-$[W]_n$- wherein X is "-O-" or "-S-" and can be modified via methods known in the art to give compounds of Formula (I), for example, via an alkylation procedure with Z-$[Y]_m$-Lg wherein Lg is a leaving group defined herein, *supra* or via the Mitsunobu reaction. In the scenario where X is "-S-", conversion can to the corresponding sulfoxide [i.e., X = -S(O)-] or sulfone [i.e., X = -$S(O)_2$-] can be implemented via oxidation, for example, mCPPA or H_2O_2. It is understood that the chemistry described for the Q group can be "reversed" or used in an "alternative" manner with the corresponding reactant. To illustrate this point, the aldehyde or ketone group can alternatively be part of the Q group and modified with a variety of amines using the similar synthetic procedures described above, such as, reductive amination (see Examples, *infra*). Likewise, in an alternative manner, Q can be Lg-$[W]_n$- and used, for example, to alkylate Z-$[Y]_m$-XH.

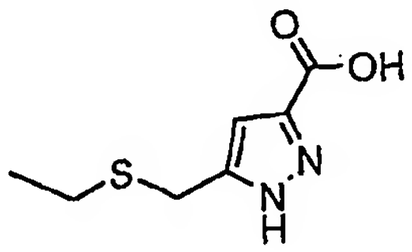
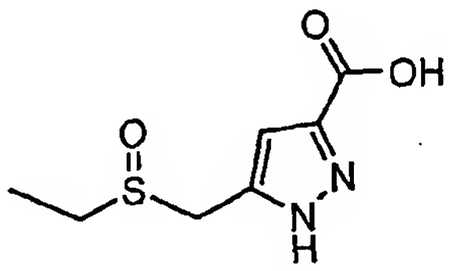
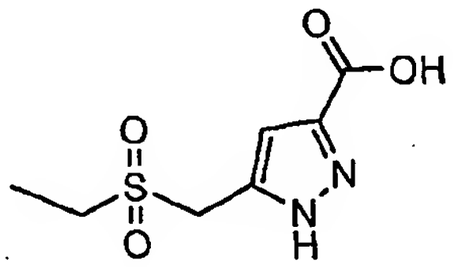
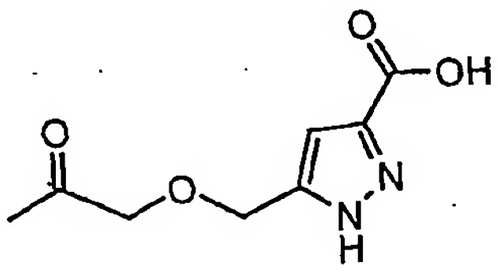
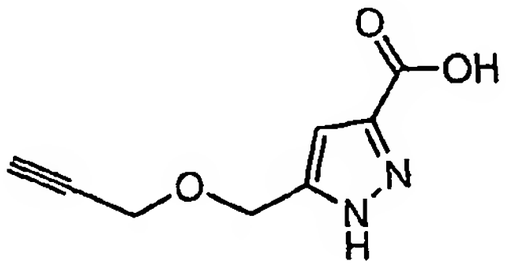
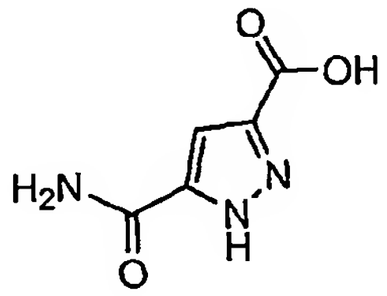
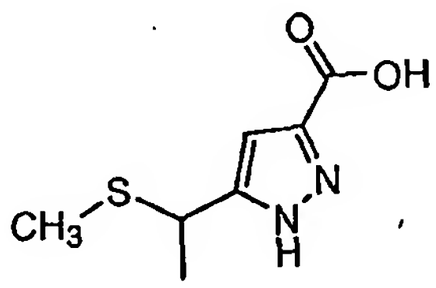
Esters of the compounds shown herein, wherein R_2 = alkyl, can be readily converted to the corresponding carboxylic acids of Formula (I) by methods known in the art, such as alkaline hydrolysis using LiOH, NaOH, KOH, and the like. Another method for the conversion of an ester to a carboxylic acid of Formula (I) is through the use of acid hydrolysis, such as aqueous HCl and the like. Generally, the solvent is an aqueous mixture with a polar solvent as described above.

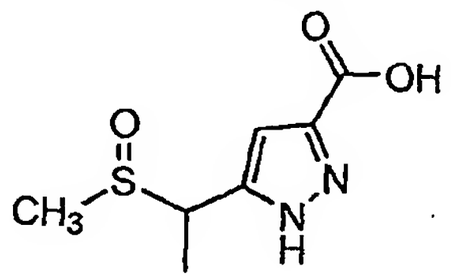
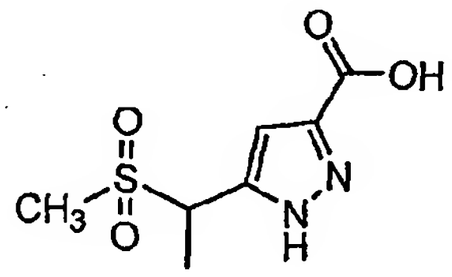
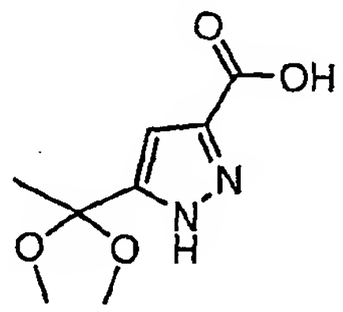
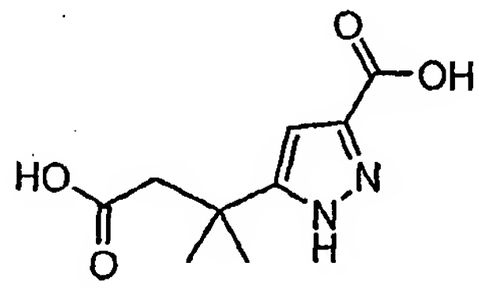
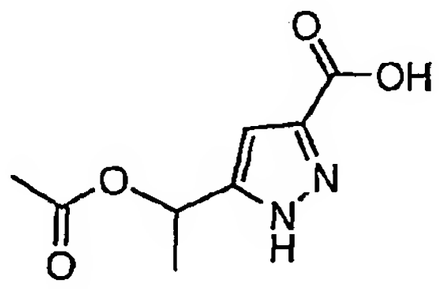
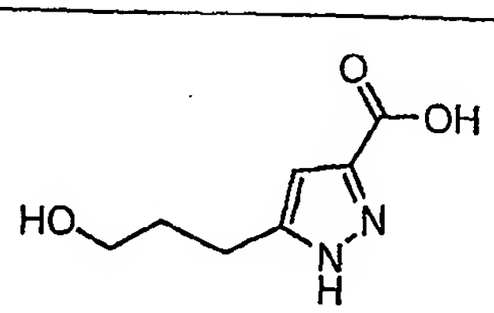
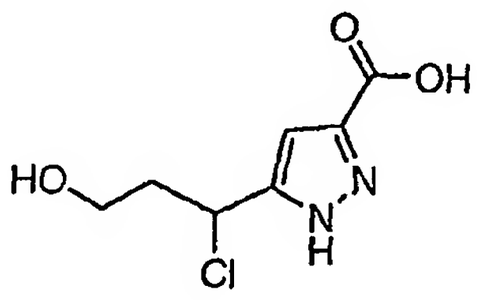
The various organic group transformations and protecting groups utilized herein can be performed by a number of procedures other than those described above. References for other synthetic procedures that can be utililized for the preparation of intermediates or compounds disclosed herein can be found in, for example, Smith, M. B.; and March, J., *Advanced Organic Chgemistry*, 5th Edition, Wiley-Interscience (2001); Larock, R.C., *Comprehensive Organic Transformations, A Guide to Functional Group Preparations*, 2nd Edition, VCH Publishers, Inc. (1999), or Wuts, P. G. M.; Greene, T. W.; *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley and Sons, (1999), all three incorporated in their entirety herein by reference.

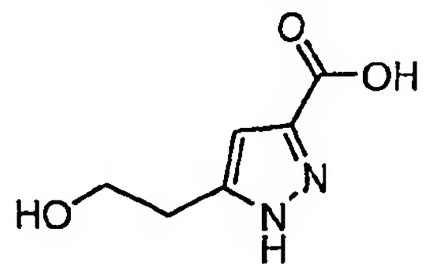
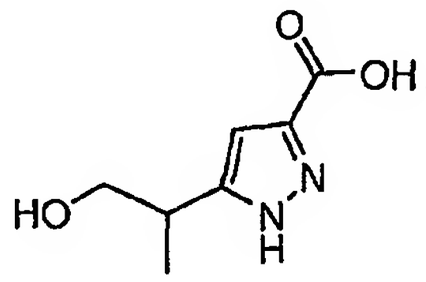
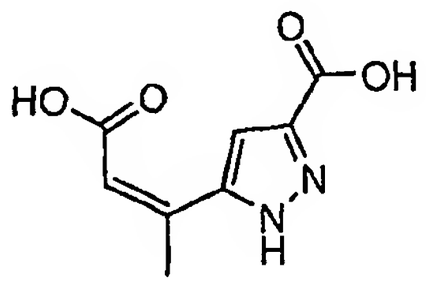
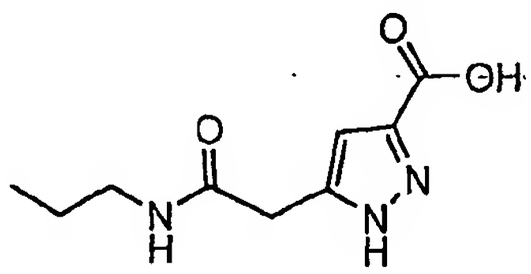
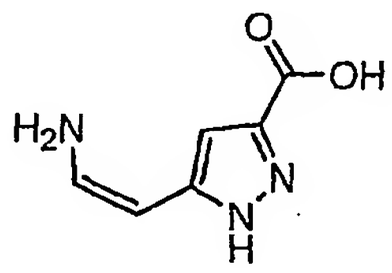
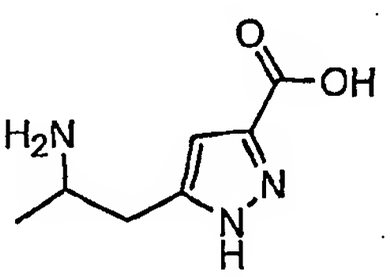
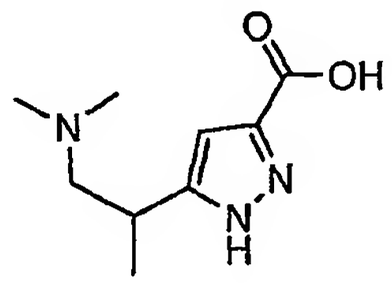
It is understood that the chemistry described here is representative and is not intended to be limiting in any manner.

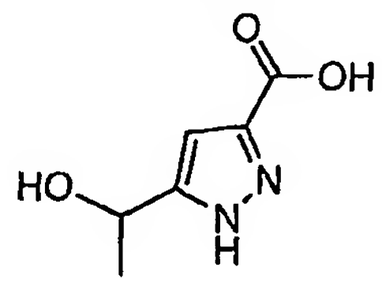
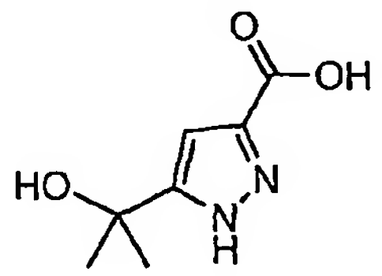
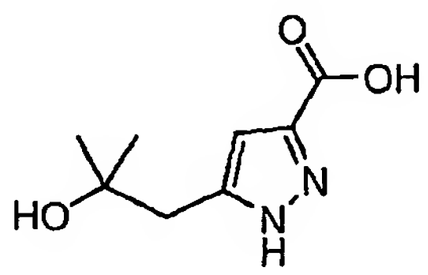
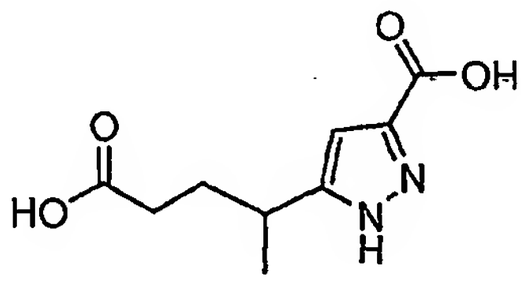
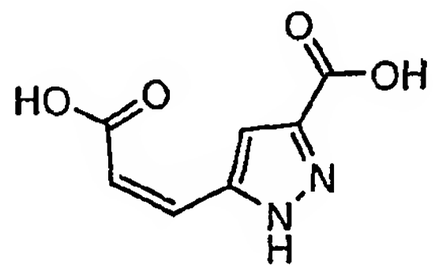
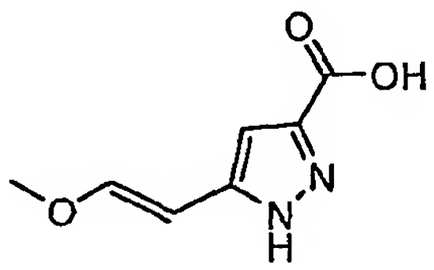
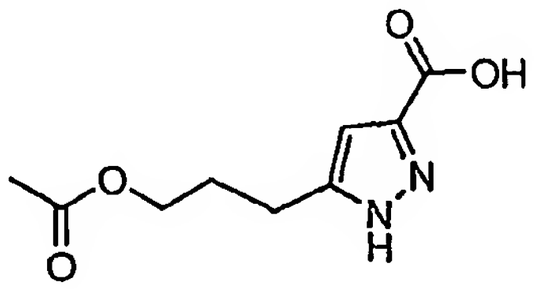
Representative examples of compound of Formula (I) are shown below in TABLE A.

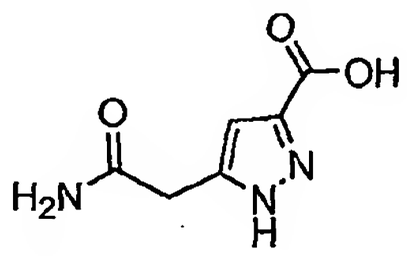
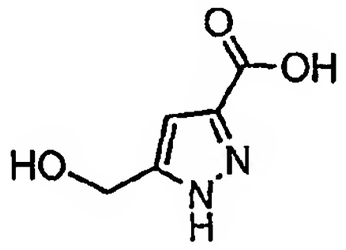
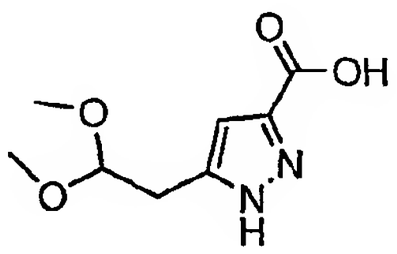
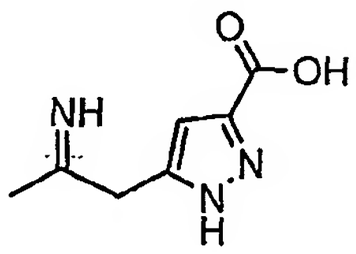
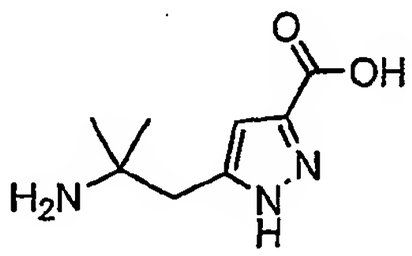
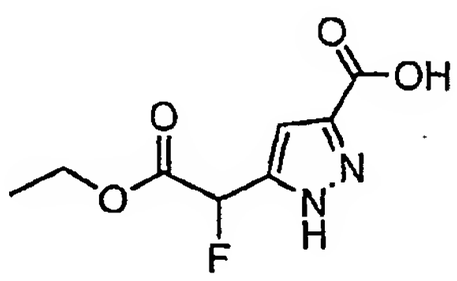
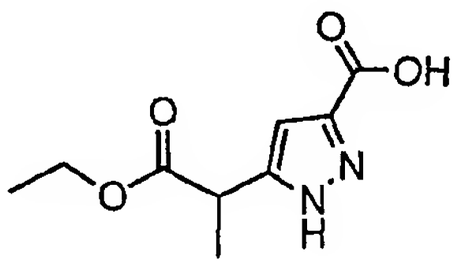
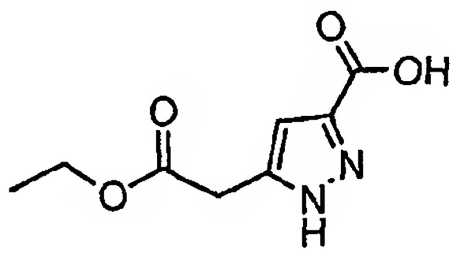
TABLE A

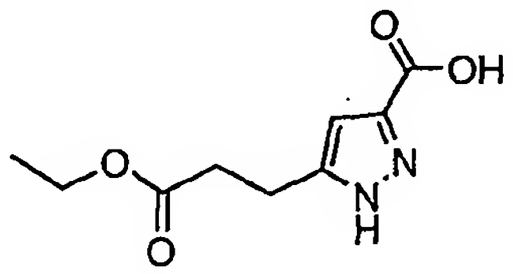
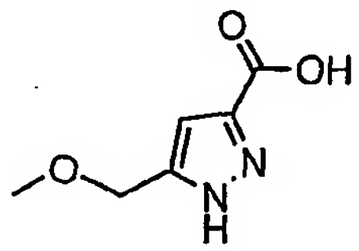
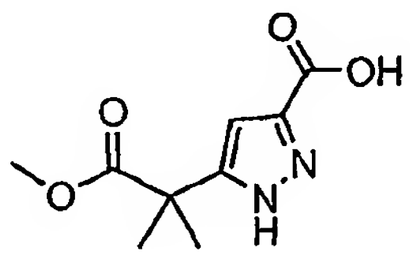
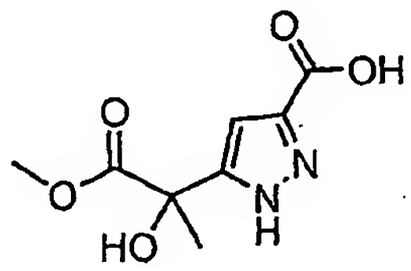
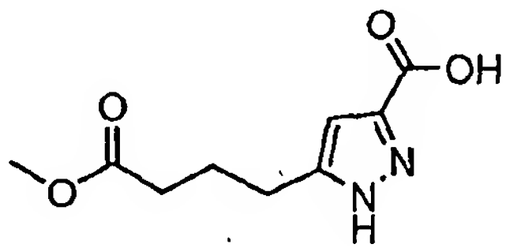
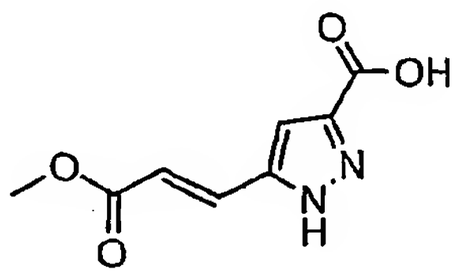
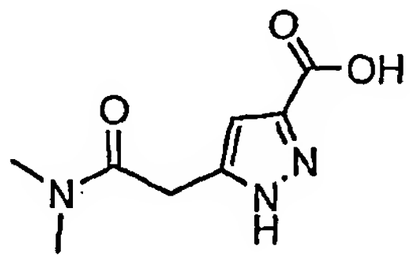
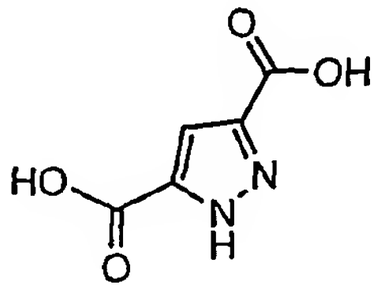
Cmpd#	Structure	Chemical Name
1		5-Ethylsulfanylmethyl-1H-pyrazole-3-carboxylic acid
2		5-Ethanesulfinylmethyl-1H-pyrazole-3-carboxylic acid
3		5-Ethanesulfonylmethyl-1H-pyrazole-3-carboxylic acid
4		5-(2-Oxo-propoxymethyl)-1H-pyrazole-3-carboxylic acid
5		5-Prop-2-ynyloxymethyl-1H-pyrazole-3-carboxylic acid
6		5-Carbamoyl-1H-pyrazole-3-carboxylic acid
7		5-(1-Methylsulfanyl-ethyl)-1H-pyrazole-3-carboxylic acid

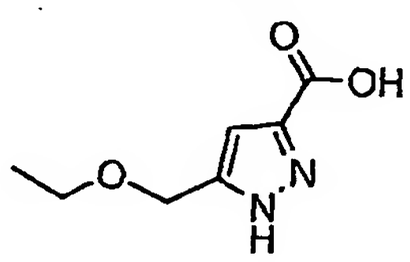
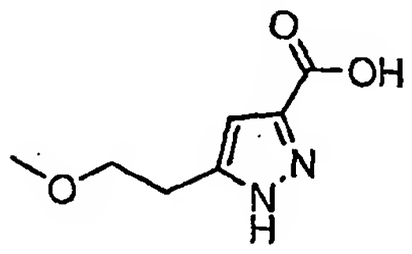
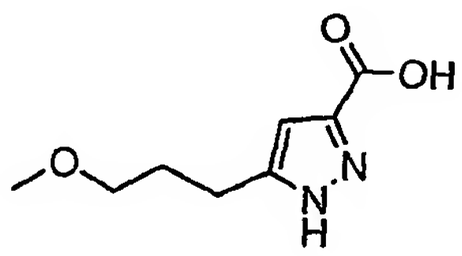
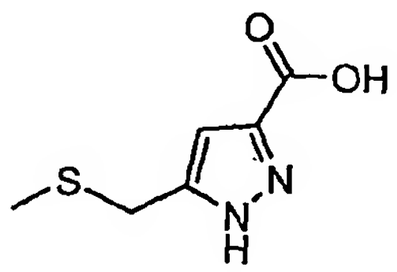
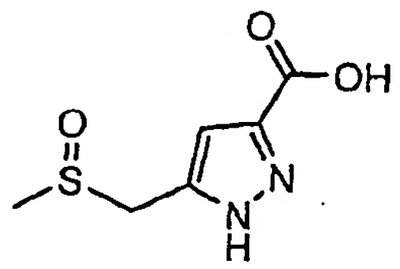
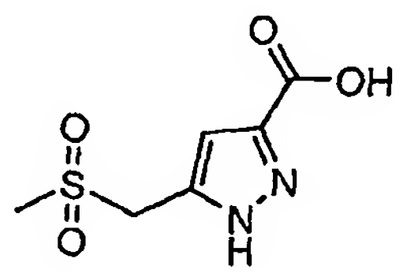
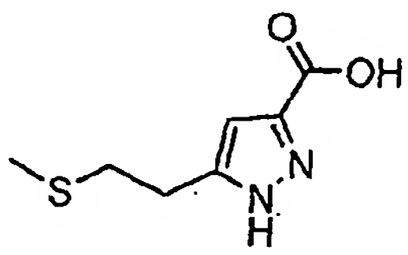
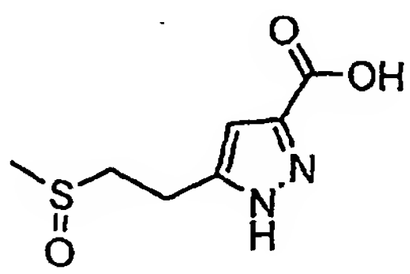
Cmpd#	Structure	Chemical Name
8		5-(1-Methanesulfinyl-ethyl)-1H-pyrazole-3-carboxylic acid
9		5-(1-Methanesulfonyl-ethyl)-1H-pyrazole-3-carboxylic acid
10		5-(1,1-Dimethoxy-ethyl)-1H-pyrazole-3-carboxylic acid
11		5-(2-Carboxy-1,1-dimethyl-ethyl)-1H-pyrazole-3-carboxylic acid
12		5-(1-Acetoxy-ethyl)-1H-pyrazole-3-carboxylic acid
13		5-(3-Hydroxy-propyl)-1H-pyrazole-3-carboxylic acid
14		5-(1-Chloro-3-hydroxy-propyl)-1H-pyrazole-3-carboxylic acid

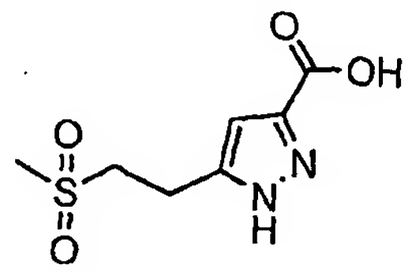
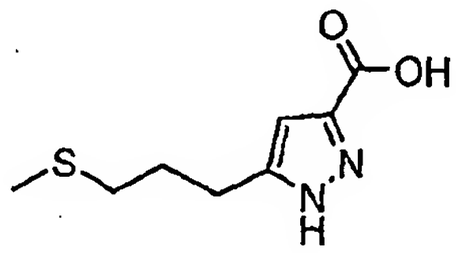
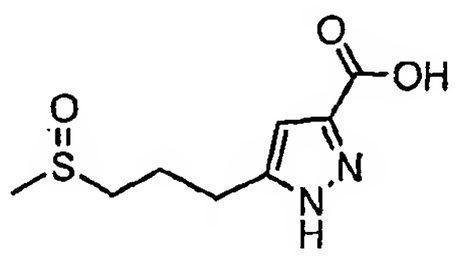
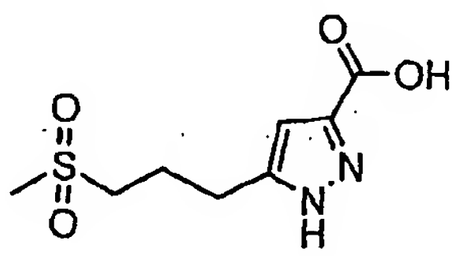
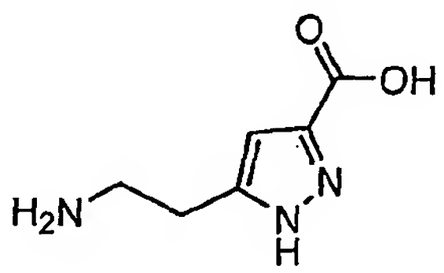
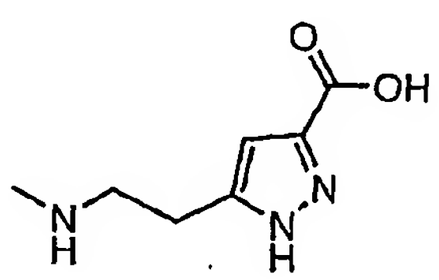
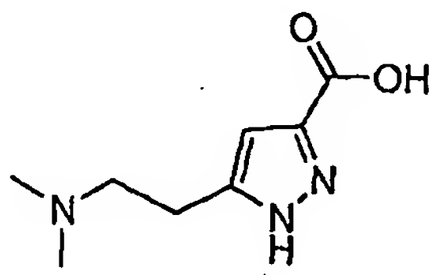
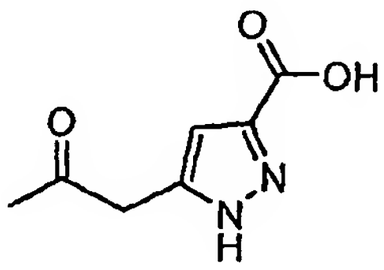
Cmpd#	Structure	Chemical Name
15		5-(2-Hydroxy-ethyl)-1H-pyrazole-3-carboxylic acid
16		5-(2-Hydroxy-1-methyl-ethyl)-1H-pyrazole-3-carboxylic acid
17		5-(2-Carboxy-1-methyl-vinyl)-1H-pyrazole-3-carboxylic acid
18		5-Propylcarbamoylmethyl-1H-pyrazole-3-carboxylic acid
19		5-(2-Amino-vinyl)-1H-pyrazole-3-carboxylic acid
20		5-(2-Amino-propyl)-1H-pyrazole-3-carboxylic acid
21		5-(2-Dimethylamino-1-methyl-ethyl)-1H-pyrazole-3-carboxylic acid

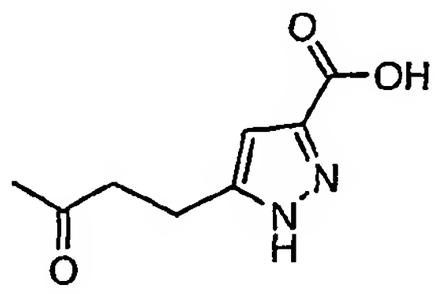
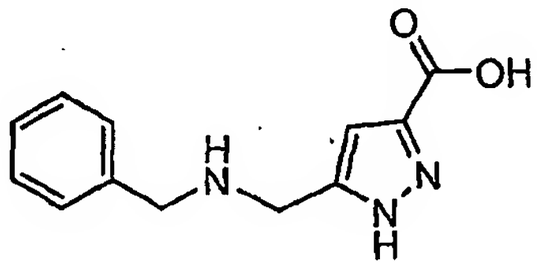
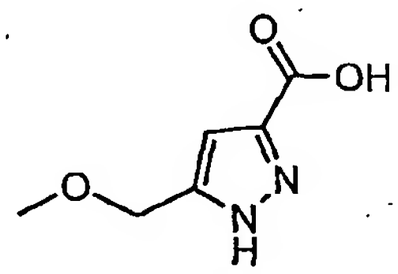
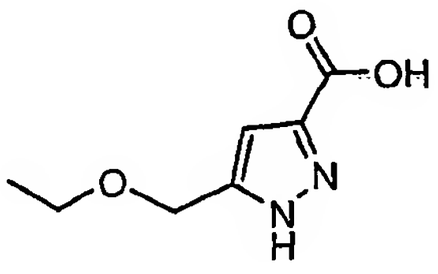
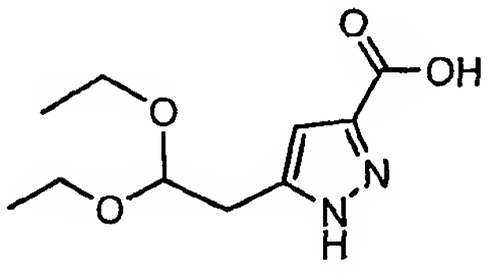
Cmpd#	Structure	Chemical Name
22		5-(1-Hydroxy-ethyl)-1H-pyrazole-3-carboxylic acid
23		5-(1-Hydroxy-1-methyl-ethyl)-1H-pyrazole-3-carboxylic acid
24		5-(2-Hydroxy-2-methyl-propyl)-1H-pyrazole-3-carboxylic acid
25		5-(3-Carboxy-1-methyl-propyl)-1H-pyrazole-3-carboxylic acid
26		5-(2-Carboxy-vinyl)-1H-pyrazole-3-carboxylic acid
27		5-(2-Methoxy-vinyl)-1H-pyrazole-3-carboxylic acid
28		5-(3-Acetoxy-propyl)-1H-pyrazole-3-carboxylic acid

Cmpd#	Structure	Chemical Name
29		5-Carbamoylmethyl-1H-pyrazole-3-carboxylic acid
30		5-Hydroxymethyl-1H-pyrazole-3-carboxylic acid
31		5-(2,2-Dimethoxy-ethyl)-1H-pyrazole-3-carboxylic acid
32		5-(2-Imino-propyl)-1H-pyrazole-3-carboxylic acid
33		5-(2-Amino-2-methyl-propyl)-1H-pyrazole-3-carboxylic acid
34		5-(Ethoxycarbonyl-fluoro-methyl)-1H-pyrazole-3-carboxylic acid
35		5-(1-Ethoxycarbonyl-ethyl)-1H-pyrazole-3-carboxylic acid
36		5-Ethoxycarbonylmethyl-1H-pyrazole-3-carboxylic acid

Cmpd#	Structure	Chemical Name
37		5-(2-Ethoxycarbonyl-ethyl)-1H-pyrazole-3-carboxylic acid
38		5-Methoxymethyl-1H-pyrazole-3-carboxylic acid
39		5-(1-Methoxycarbonyl-1-methyl-ethyl)-1H-pyrazole-3-carboxylic acid
40		5-(1-Hydroxy-1-methoxycarbonyl-ethyl)-1H-pyrazole-3-carboxylic acid
41		5-(3-Methoxycarbonyl-propyl)-1H-pyrazole-3-carboxylic acid
42		5-(2-Methoxycarbonyl-vinyl)-1H-pyrazole-3-carboxylic acid
43		5-Dimethylcarbamoylmethyl-1H-pyrazole-3-carboxylic acid
44		1H-Pyrazole-3,5-dicarboxylic acid

Cmpd#	Structure	Chemical Name
45		5-Ethoxymethyl-1H-pyrazole-3-carboxylic acid
46		5-(2-Methoxy-ethyl)-1H-pyrazole-3-carboxylic acid
47		5-(3-Methoxy-propyl)-1H-pyrazole-3-carboxylic acid
48		5-Methylsulfanylmethyl-1H-pyrazole-3-carboxylic acid
49		5-Methanesulfinylmethyl-1H-pyrazole-3-carboxylic acid
50		5-Methanesulfonylmethyl-1H-pyrazole-3-carboxylic acid
51		5-(2-Methylsulfanyl-ethyl)-1H-pyrazole-3-carboxylic acid
52		5-(2-Methanesulfinyl-ethyl)-1H-pyrazole-3-carboxylic acid

Cmpd#	Structure	Chemical Name
53		5-(2-Methanesulfonyl-ethyl)-1H-pyrazole-3-carboxylic acid
54		5-(3-Methylsulfanyl-propyl)-1H-pyrazole-3-carboxylic acid
55		5-(3-Methanesulfinyl-propyl)-1H-pyrazole-3-carboxylic acid
56		5-(3-Methanesulfonyl-propyl)-1H-pyrazole-3-carboxylic acid
57		5-(2-Amino-ethyl)-1H-pyrazole-3-carboxylic acid
58		5-(2-Methylamino-ethyl)-1H-pyrazole-3-carboxylic acid
59		5-(2-Dimethylamino-ethyl)-1H-pyrazole-3-carboxylic acid
60		5-(2-Oxo-propyl)-1H-pyrazole-3-carboxylic acid

Cmpd#	Structure	Chemical Name
61		5-(3-Oxo-butyl)-1H-pyrazole-3-carboxylic acid
62		5-(Benzylamino-methyl)-1H-pyrazole-3-carboxylic acid
63		5-Methoxymethyl-1H-pyrazole-3-carboxylic acid
64		5-Ethoxymethyl-1H-pyrazole-3-carboxylic acid
65		5-(2,2-Diethoxy-ethyl)-1H-pyrazole-3-carboxylic acid

It is understood that the present invention includes compounds shown in TABLE A and corresponding tautomers and esters thereof.

Compositions of the Present Invention

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

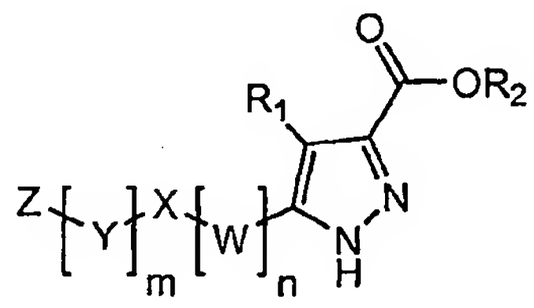
Formulations can be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants, and disintegrants can be used in tablets and capsules for oral

administration. Liquid preparations for oral administration can be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations can be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants can be added to the liquid preparations. Parenteral dosage forms can be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, The Science and Practice of Pharmacy, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro, A. R., et al.).

While it is possible that a compound for use in the prophylaxis or treatment of the present invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or "active ingredient" as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier. Therefore, one aspect of the present invention encompasses pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with at least one compound according to Formula (I):



(I)

wherein:

W and Y are independently a straight or branched chain C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl or C_{1-4} alkoxy;

X is $-NR_3C(O)-$, $-C(O)NR_3$, $-NR_3S(O)_2-$, $-S(O)_2NR_3-$, $-NR_3C(O)NR_4-$, $-NR_3C(O)O-$, $-OC(O)NR_3-$, $-NR_3-$, $-C(O)-$, $-CH(OH)-$, $-C(NH)-$, $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

R_3 and R_4 are independently H, C_{1-4} alkyl, phenyl or heteroaryl, wherein each of the alkyl, phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4}

alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

Z is H, halogen, phenyl or heteroaryl, wherein said phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxy, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

R_1 is H, hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R_2 is H or C_{1-8} alkyl and

"n" and "m" are each independently 0 or 1; or

a pharmaceutically acceptable salt, solvate or hydrate thereof;

provided that when X is $-NR_3-$ then "n" is 1.

Applicant reserves the right to exclude one or more of the compounds from any pharmaceutical composition embodiment; for example, one or more compounds can be excluded from any pharmaceutical composition embodiment selected from the group consisting of:

i) R_1 and R_2 are both H and $-[W]_n-X-[Y]_m-Z$ together is selected from the group consisting of: CO_2H, $C(O)-C_6H_4-p-O-C_8H_{17}$, OCH_2CH_3, OH, $CH_2CH_2CH_2CH_2CO_2H$, $CH_2CH_2CH_2CO_2H$, CH_2CO_2H and $CH_2CH_2CO_2H$;

ii) R_1 is CH_3, R_2 is H and $-[W]_n-X-[Y]_m-Z$ together is selected from the group consisting of CH_2CO_2H, $C(O)CH{=}CH\ C_6H_5$, $C(O)C_6H_4-p-OCH_3$, CO_2H, $C(O)CH_3$, $C(O)C_6H_4-o-CH_3$, $C(O)C_6H_4-o-Br$, $C(O)C_6H_4-o-Cl$, and $C(O)C_6H_5$;

iii) R_1 is Br, R_2 is H and $-[W]_n-X-[Y]_m-Z$ together is CO_2H;

iv) R_1 is OH, R_2 is H and $-[W]_n-X-[Y]_m-Z$ together is CO_2H;

v) R_1 is H, R_2 is CH_3 and $-[W]_n-X-[Y]_m-Z$ together is selected from the group consisting of 2,6-dichloro-4-trifluoromethylphenoxy, $C(O)NH-C_6H_4-p-OCH_2CH_3$, $NHC(O)CH(CH_3)_2$, SCH_3, $C(O)-C_6H_4-p-O-C_8H_{17}$, SCH_2CH_3, $C(O)NHC_6H_5$, $CH(OCH_3)_2$, $CH_2OC(O)CH_3$, CO_2H, CO_2CH_3, $C(O)C_6H_4-p-NO_2$, $C(O)C_6H_5$, $CH_2CH_2CO_2CH_3$, $CH_2CH_2CH_2CH_2CO_2CH_3$, $CH_2CH_2CH_2CO_2CH_3$ and $CH_2CO_2CH_3$;

vi) R_1 is OH, R_2 is CH_3 and $-[W]_n-X-[Y]_m-Z$ together is selected from the group consisting of $CH_2OCH_2C_6H_5$, $CH_2OCH(CH_3)_2$ and CH_2OH;

vii) R_2 is CH_3:

R_1 is CH_3 and $-[W]_n-X-[Y]_m-Z$ together is 2,6-dichloro-4-trifluoromethylphenoxy;

R_1 is I and $-[W]_n-X-[Y]_m-Z$ together is $CO_2C(CH_3)_3$;

R_1 is $C(CH_3)_3$ and $-[W]_n$-X-$[Y]_m$-Z together is formyl;

R_1 is Br and $-[W]_n$-X-$[Y]_m$-Z together is CO_2CH_3;

and

R_1 is $CH_2CH_2CH_2CH_3$ and $-[W]_n$-X-$[Y]_m$-Z together is formyl;

viii) R_1 is H; R_2 is CH_2CH_3 and $-[W]_n$-X-$[Y]_m$-Z together is selected from the group consisting of $CH_2SCH_2CH_3$, $OCH_2CH_2CH=CH_2$, $CH_2CH_2CH_2OH$, CH_2CH_2CHO, $CO_2CH_2CH_3$, OCH_3, $C(O)CH_2Br$, $CO_2C_8H_{17}$, formyl, OH, $CH_2N(CH_2CH_2Cl)_2$, $CH(CH_3)OC(O)CH_3$, CH_2OH, $CH_2OC(O)CH_3$, $C(O)CH_3$, $C(O)C_6H_5$ and $C(O)NHCH_2CO_2CH_2CH_3$.

ix) R_1 is CH_3, R_2 is CH_2CH_3 and $-[W]_n$-X-$[Y]_m$-Z together is selected from the group consisting of $CH(OH)C_6H_4$-*p*-$N(CH_3)_2$, $C(O)CH_2C(O)CH_3$, $CO_2CH_2C_6H_5$, CO_2CH_3, $C(O)CH_2CH_2CH_3$, $C(O)CH_3$, $C(O)C_6H_4$-*p*-OCH_3, $C(O)C_6H_4$-*o*-Br, $C(O)C_6H_4$-*p*-Cl, $C(O)C_6H_4$-*o*-Cl, $C(O)CH_2C_6H_5$ and $C(O)C_6H_5$;

x) R_2 is CH_2CH_3:

R_1 is I and $-[W]_n$-X-$[Y]_m$-Z together is $CO_2CH_2CH_3$;

R_1 is CF_3 and $-[W]_n$-X-$[Y]_m$-Z together is $CO_2CH_2CH_3$; and

R_1 is Br and $-[W]_n$-X-$[Y]_m$-Z together is $CO_2CH_2CH_3$;

xi) R_1 is OH, R_2 is CH_2CH_3 and $-[W]_n$-X-$[Y]_m$-Z together is selected from the group consisting of $C(O)C_6H_5$, $C(O)NH_2$ and $CO_2CH_2CH_3$;

xii) R_1 is H, R_2 is $C(CH_3)_3$ and $-[W]_n$-X-$[Y]_m$-Z together is selected from the group consisting of $CO_2C(CH_3)_3$, $C(O)NHC(O)CH_3$ and $C(O)NH_2$; and

xiii) R_1 is OH, R_2 is $CH_2CH_2CH_2CH_3$ and $-[W]_n$-X-$[Y]_m$-Z together is $C(O)C_6H_5$.

While it is possible that a compound of the invention may, in an alternative mode, be administered as a raw or pure chemical, it is preferable to present the compound or "active ingredient" as a pharmaceutical formulation or composition.

The invention provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum

of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form can be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition can be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water can be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as RUP25 receptor agonists. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention.

Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 to about 2500 mg, about 0.001 to about 1000 mg, 0.001 to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg, and about 0.001 mg to about 25 mg. Multiple doses can be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in prophylaxis or treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system to another, for example, an animal model to a human. Typically, animal models include, but are not limited to, the rodents diabetes models as described in Example 15, *infra*; the mouse artherosclerosis model as described in Example 16, *infra*; or the *in vivo* animal arthosclerosis model as described in Example 17, *infra*. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weight differences, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the Formula (I) and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors, such as, those cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, can be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself can be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations.

If appropriate, depending on individual behavior, it can be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desire shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and can be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention can be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions can be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges

comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations can be provided in single or multi-dose form. In the latter case of a dropper or pipette, this can be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this can be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the Formula (**I**) or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the Formula (**I**) as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the Formula (**I**) in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug can be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size can be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient can be employed.

Alternatively the active ingredients can be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition can be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder can be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form,

the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In general, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Combination Therapy - Prophylaxis and Treatment:

While the compounds of the present invention can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), they can also be used in combination with other pharmaceutical agents (i.e., combination-therapy), such as, for the treatment of the diseases/conditions/disorders described herein. Therefore, another aspect of the present invention includes methods of prophylaxis and/or treatment of metabolic related diseases comprising administering to an individual in need of such prophylaxis and/or treatment a therapeutically effective amount of a compound of the present invention in combination with one or more additional pharmaceutical agent as described herein.

Suitable pharmaceutical agents that can be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example, sibutramine), sympathomimetic agensts, β_3 adrenergic receptor agonists, dopamine agonists (for example, bromocriptine), melanocyte-stimulating hormone receptor analogs, cannabinoid 1 receptor antagonists [for example, SR141716: *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide], melanin

concentrating hormone antagonists, leptons (the OB protein), leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e., Orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analogue thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neutrotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or reverse agonists, neuromedin U receptor agonists, noradrenergic anorectic agents (for example, phentermine, mazindol and the like) and appetite suppressants (for example, bupropion).

Other anti-obesity agents, including the agents set forth *infra*, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

In some embodiments, the anti-obesity agents are selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, and pseudoephedrine. In a further embodiment, compounds of the present invention and combination therapies are administered in conjunction with exercise and/or a sensible diet.

It is understood that the scope of combination-therapy of the compounds of the present invention with other anti-obesity agents, anorectic agents, appetite suppressant and related agents is not limited to those listed above, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of overweight and obese individuals.

Other suitable pharmaceutical agents, in addition to anti-obesity agents, that can be used in combination with the compounds of the present invention include agents useful in the prophylaxis or treatment of concomitant disorders. Treatment of such disorders include the use of one or more pharmaceutical agents known in the art that belong to the classes of drugs referred to, but not limited to, the following: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists, insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and adiponectin. In accordance to one aspect of the present invention, a compound of the present can be used in combination with a pharmaceutical agent or agents belonging to one or more of the classes of drugs cited herein.

It is understood that the scope of combination-therapy of the compounds of the present invention with other pharmaceutical agents is not limited to those listed herein, *supra* or *infra*, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of diseases, conditions or disorders that are linked to metabolic-related disorders.

Some embodiments of the present invention include methods of prophylaxis or treatment of a disease, disorder or condition as described herein comprising administering to an individual in need of such prophylaxis or treatment a therapeutically effect amount or dose of a compound of the present invention in combination with at least one pharmaceutical agent selected from the group consisting of: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists, insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and adiponectin. In some embodiments, the pharmaceutical composition further comprises one or more agents selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

One aspect of the present invention encompasses pharmaceutical compositions comprising at least one compound according to Formula (**I**), as described herein. In some embodiments, the pharmaceutical composition further comprises one or more agents selected from the group consisting of, for example, α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include α-glucosidase inhibitors. α-Glucosidase inhibitors belong to the class of drugs which competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in the pancreas and or small intesting. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Some representative examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include sulfonylureas. The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the sulfonylureas include glyburide , glipizide, glimepiride and other sulfonylureas known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the meglitinides. The meglitinides are benzoic acid derivatives represent a novel class of insulin secretagogues. These agents target postprandial hyperglycemia and show comparable efficacy to sulfonylureas in reducing HbA_{1c}. Examples of meglitinides include repaglinide, nateglinide and other meglitinides known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the biguanides. The biguanides represent a class of drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress of hepatic gluconeogenesis, and inhibit fatty acid oxidation. Examples of biguanides include phenformin, metformin, buformin, and biguanides known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the α-glucosidase inhibitors. The α-glucosidase inhibitors competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in the pancreas and or small intestine. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists. The peroxisome proliferators-activated receptor-γ agonists represent a class of compounds that activates the nuclear receptor PPAR-γ and therefore regulate the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Agents in the class also facilitate the regulation of fatty acid metabolism. Examples of PPAR-γ agonists include rosiglitazone, pioglitazone, tesaglitazar, netoglitazone, GW-409544, GW-501516 and PPAR-γ agonists known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the HMG-CoA reductase inhibitors. The HMG-CoA reductase inhibitors are agents also referred to as Statin compounds that belong to a class of drugs that lower blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA)

reductase. HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. The statins lower serum LDL concentrations by upregulating the activity of LDL receptors and are responsible for clearing LDL from the blood. Some representative examples the statin compounds include rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, BMS's "superstatin", and HMG-CoA reductase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the angiotensin converting enzyme (ACE) inhibitors. The angiotensin converting enzyme inhibitors belong to the class of drugs that partially lower blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, and angiotensin converting enzyme inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the angiotensin II receptor antagonists. Angiotensin II receptor antagonists target the angiotensin II receptor subtype 1 (i.e., AT1) and demonstrate a beneficial effect on hypertension. Examples of angiotensin II receptor antagonists include losartan (and the potassium salt form), and angiotensin II receptor antagonists known in the art.

Other treatments for one or more of the diseases cited herein include the use of one or more pharmaceutical agents known in the art that belong to the classes of drugs referred to, but not limited to, the following: amylin agonists (for example, pramlintide), insulin secretagogues (for example, GLP-1 agonists; exendin-4; insulinotropin (NN2211); dipeptyl peptidase inhibitors (for example, NVP-DPP-728), acyl CoA cholesterol acetyltransferase inhibitors (for example, Ezetimibe, eflucimibe, and like compounds), cholesterol absorption inhibitors (for example, ezetimibe, pamaqueside and like compounds), cholesterol ester transfer protein inhibitors (for example, CP-529414, JTT-705, CETi-1, and like compounds), microsomal triglyceride transfer protein inhibitors (for example, implitapide, and like compounds), cholesterol modulators (for example, NO-1886, and like compounds), bile acid modulators (for example, GT103-279 and like compounds) and squalene synthase inhibitors. Squalene synthesis inhibitors belong to a class of drugs that lower blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494) and squalene synthesis inhibitors known in the art.

In accordance with the present invention, the combination can be used by mixing the

respective active components either all together or independently with a pharmaceutically acceptable carrier, excipient, binder, diluent, etc., as described herein above, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When a compound or a mixture of compounds of Formula (**I**) are administered as a combination therapy or prophylaxis with another active compound the therapeutic agents can be formulated as separate pharmaceutical compositions given at the same time or at different times, or the therapeutic agents can be given as a single composition.

In accordance with the present invention, the combination of a compound of the present invention and pharmaceutical agent can be prepared by mixing the respective active components either all together or independently with a pharmaceutically acceptable carrier, excipient, binder, diluent, etc., as described herein, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When a compound or a mixture of compounds of Formula (**I**) are administered as a combination therapy or prophylaxis with another active compound the therapeutic agents can be formulated as a separate pharmaceutical compositions given at the same time or at different times, or the therapeutic agents can be given as a single composition.

Other Utilities

Another object of the present invention relates to radio-labeled compounds of Formula (**I**) that are useful not only in radio-imaging but also in assays, both in vitro and in vivo, for localizing and quantitating RUP25 in tissue samples, including human, and for identifying RUP25 ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to include novel RUP25 assays of which comprise such radio-labeled compounds.

The present invention embraces isotopically-labeled compounds of Formula (**I**) and any subgenera herein, such as but not limited to, Formulae (**Ia**) to (**Iz**); (**IIa**) to (**IIy**); (**IIIa**) to (**IIIt**); and (**IVa**) to (**IVs**). An "isotopically" or "radio-labeled" compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that can be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* **RUP25** labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I, or ^{35}S will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br,

^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled " or "labeled compound" is a compound of Formula (I) that has incorporated at least one radionuclide; in some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I, ^{35}S and ^{82}Br.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ^{3}H and/or ^{14}C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence can be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes *supra* and Examples *infra*, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed *infra*. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the more scarce radio-isotope or nonradio-active isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, and are as follows:

A. Catalytic Reduction with Tritium Gas - This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [^{3}H] - This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

C. Reduction with Lithium Aluminum Hydride [^{3}H] - This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

D. Tritium Gas Exposure Labeling - This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. N-Methylation using Methyl Iodide [^{3}H] - This procedure is usually employed to prepare O-methyl or N-methyl (^{3}H) products by treating appropriate precursors with high specific activity methyl iodide (^{3}H). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

A. Sandmeyer and like reactions – This procedure transforms an aryl or heteroaryl

amine into a diazonium salt, such as a tetrafluoroborate salt, and subsequently to ^{125}I labeled compound using $Na^{125}I$. A represented procedure was reported by Zhu, D.-G. and co-workers in *J. Org. Chem.* **2002**, *67*, 943-948.

B. Ortho ^{125}Iodination of phenols – This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labeled Compd Radiopharm.* **1999**, *42*, S264-S266.

C. Aryl and heteroaryl bromide exchange with ^{125}I – This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $Pd(Ph_3P)_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(CH_3)_3SnSn(CH_3)_3$]. A represented procedure was reported by Bas, M.-D. and co-workers in *J. Labeled Compd Radiopharm.* **2001**, *44*, S280-S282.

A radio-labeled RUP25 compound of Formula (**I**) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the "radio-labeled compound of Formula (**I**)" to the RUP25 receptor. Accordingly, the ability of a test compound to compete with the "radio-labeled compound of Formula (**I**)" for the binding to the RUP25 receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the RUP25 receptor. In one embodiment, the labeled compound has an IC_{50} less than about 500 μM, in another embodiment the labeled compound has an IC_{50} less than about 100 μM, in yet another embodiment the labeled compound has an IC_{50} less than about 10 μM, in yet another embodiment the labeled compound has an IC_{50} less than about 1 μM, and in still yet another embodiment the labeled inhibitor has an IC_{50} less than about 0.1 μM.

Other uses of the disclosed receptors and methods will become apparent to those in the art based upon, inter alia, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

The following Examples are provided for illustrative purposes and not as a means of limitation. One of ordinary skill in the art would be able to design equivalent assays and methods based on the disclosure herein, all of which form part of the present invention.

Example 1

Full Length Cloning

hRUP25

The disclosed human **hRUP25** was identified based upon the use of the GenBank database information. While searching the database, a cDNA clone with Accession Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length **hRUP25** was cloned by PCR using primers:

5'-GCTGGAGCATTCACTAGGCGAG-3' (SEQ.ID.NO.:1; sense, 5'of initiation codon),
5'-AGATCCTGGTTCTTGGTGACAATG-3' (SEQ.ID.NO.:2; antisense, 3' of stop codon)
and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from a 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystems).

Example 2

Receptor Expression

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

a. Transient Transfection

On day one, $6x10^6$/ 10 cm dish of 293 cells well were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 4μg DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 0.5 ml serum free DMEM (Gibco BRL); tube B was prepared by mixing 24μl lipofectamine (Gibco BRL) in 0.5ml serum free DMEM. Tubes A and B were admixed by

inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 5 ml serum free DMEM. 1 ml of the transfection mixture were added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture was removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO_2. After 48hr incubation, cells were harvested and utilized for analysis.

b. Stable Cell Lines: Gs Fusion Protein

Approximately $12x10^6$ 293 cells are plated on a 15cm tissue culture plate. Grown in DME High Glucose Medium containing ten percent fetal bovine serum and one percent sodium pyruvate, L-glutamine, and anti-biotics. Twenty-four hours following plating of 293 cells (or to ~80% confluency), the cells are transfected using 12μg of DNA. The 12μg of DNA is combined with 60μl of lipofectamine and 2mL of DME High Glucose Medium without serum. The medium is aspirated from the plates and the cells are washed once with medium without serum. The DNA, lipofectamine, and medium mixture are added to the plate along with 10mL of medium without serum. Following incubation at 37 degrees Celsius for four to five hours, the medium is aspirated and 25ml of medium containing serum is added. Twenty-four hours following transfection, the medium is aspirated again, and fresh medium with serum is added. Forty-eight hours following transfection, the medium is aspirated and medium with serum is added containing geneticin (G418 drug) at a final concentration of 500μg/mL. The transfected cells now undergo selection for positively transfected cells containing the G418 resistant gene. The medium is replaced every four to five days as selection occurs. During selection, cells are grown to create stable pools, or split for stable clonal selection.

EXAMPLE 3

Assays For determination of Constitutive Activity of Non-Endogenous GPCRs

A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. Membrane Binding Assays: [^{35}S]GTPγS Assay

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which

point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing constitutively activated receptors. The advantage of using [^{35}S]GTPγS binding to measure constitutive activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [^{35}S]GTPγS assay was incubated in 20 mM HEPES and between 1 and about 20mM $MgCl_2$ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [^{35}S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 µg membrane protein (*e.g.* 293 cells expressing the Gs Fusion Protein; this amount can be adjusted for optimization) and 10 µM GDP (this amount can be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 µl; Amersham) were then added and the mixture incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

2. Adenylyl Cyclase

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells were harvested approximately twenty four hours after transient transfection. Media is carefully aspirated off and discarded. 10ml of PBS is gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS are added to each plate. Cells were pipetted off the plate and the cell suspension was collected into a 50ml conical centrifuge tube. Cells were then centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet was carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells were then counted using a hemocytometer and additional PBS was added to give the appropriate number of cells (with a

final volume of about 50 µl/well).

cAMP standards and Detection Buffer [comprising 1 µCi of tracer ^{125}I-cAMP (50 µl) to 11 ml Detection Buffer] was prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 50µl of Stimulation Buffer, 3ul of test compound (12µM final assay concentration) and 50µl cells, Assay Buffer was stored on ice until utilized. The assay was initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50ul of PBSA to wells H-11 and H12. 50µl of Stimulation Buffer was added to all wells. DMSO (or selected candidate compounds) was added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells were then added to the wells and incubated for 60 min at room temperature. 100µl of Detection Mix containing tracer cAMP was then added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well were then extrapolated from a standard cAMP curve which was contained within each assay plate.

3. Cell-Based cAMP for Gi Coupled Target GPCRs

TSHR is a Gs coupled GPCR that causes the accumulation of cAMP upon activation. TSHR will be constitutively activated by mutating amino acid residue 623 (*i.e.*, changing an alanine residue to an isoleucine residue). A Gi coupled receptor is expected to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique for measuring the decrease in production of cAMP as an indication of constitutive activation of a Gi coupled receptor can be accomplished by co-transfecting, most preferably, non-endogenous, constitutively activated TSHR (TSHR-A623I) (or an endogenous, constitutively active Gs coupled receptor) as a "signal enhancer" with a Gi linked target GPCR to establish a baseline level of cAMP. Upon creating a non-endogenous version of the Gi coupled receptor, this non-endogenous version of the target GPCR is then co-transfected with the signal enhancer, and it is this material that can be used for screening. We will utilize such approach to effectively generate a signal when a cAMP assay is used; this approach is preferably used in the direct identification of candidate compounds against Gi coupled receptors. It is noted that for a Gi coupled GPCR, when this approach is used, an inverse agonist of the target GPCR will increase the cAMP signal and an agonist will decrease the cAMP signal.

On day one, $2X10^4$ 293 cells/well will be plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 2µg DNA of each receptor transfected into the mammalian cells, for a total of 4µg DNA (*e.g.*, pCMV vector; pCMV vector with mutated THSR (TSHR-A623I);

TSHR-A623I and GPCR, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120µl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B will then be admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells will be washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture will then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO_2. After 24hr incubation, cells will then be harvested and utilized for analysis.

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is designed for cell-based assays, however, can be modified for use with crude plasma membranes depending on the need of the skilled artisan. The Flash Plate wells will contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells will be harvested approximately twenty four hours after transient transfection. Media will be carefully aspirated off and discarded. 10ml of PBS will be gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS will be added to each plate. Cells will be pipetted off the plate and the cell suspension will be collected into a 50ml conical centrifuge tube. Cells will then be centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet will be carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells will then be counted using a hemocytometer and additional PBS is added to give the appropriate number of cells (with a final volume of about 50µl/well).

cAMP standards and Detection Buffer [comprising 1 µCi of tracer ^{125}I-cAMP (50 µl) to 11 ml Detection Buffer] will be prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer should be prepared fresh for screening and contained 50µl of Stimulation Buffer, 3µl of test compound (12µM final assay concentration) and 50µl cells, Assay Buffer can be stored on ice until utilized. The assay can be initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50µl of PBSA to wells H-11 and H12. Fifty µl of Stimulation Buffer will be added to all wells. Selected compounds (*e.g.*, TSH) will be added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells will then be added to the wells and

incubated for 60 min at room temperature. 100µl of Detection Mix containing tracer cAMP will then be added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well will then be extrapolated from a standard cAMP curve which is contained within each assay plate.

EXAMPLE 4

Tissue Distribution of the disclosed human GPCRs

A. RT-PCR

RT-PCR was applied to confirm the expression and to determine the tissue distribution of several novel human GPCRs. Oligonucleotides utilized were GPCR-specific and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) were utilized for the amplification in a 40µl reaction according to the manufacturer's instructions. 20µl of the reaction will be loaded on a 1.5% agarose gel to analyze the RT-PCR products. Table B below lists the receptors, the cycle conditions and the primers utilized.

TABLE B

Receptor Identifier	Cycle Conditions Min (‘), Sec (“) Cycles 2-4 repeated 30 times	5’ Primer (SEQ.ID.NO.)	3’ Primer (SEQ.ID.NO.)	DNA Fragment	Tissue Expression
hRUP25	96° for 2’ 96° for 30” 55°C for 1’ 72° for 2’ 72° for 10’	CTGATGGA CAACTATGT GAGGCGTT GG (3)	GCTGAAGC TGCTGCAC AAATTTGC ACC (4)	297bp	Adipocyte, spleen, leukocyte, kidney, lung, testis

Diseases and disorders related to receptors located in these tissues or regions include, but are not limited to, cardiac disorders and diseases (e.g. thrombosis, myocardial infarction; atherosclerosis; cardiomyopathies); kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic type 2 diabetes insipidus; cystinuria; polycystic kidney disease); eosinophilia; leukocytosis; leukopenia; ovarian cancer; sexual dysfunction;

polycystic ovarian syndrome; pancreatitis and pancreatic cancer; irritable bowel syndrome; colon cancer; Crohn's disease; ulcerative colitis; diverticulitis; Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis; pneumonia; pulmonary hypertension; tuberculosis and lung cancer; Parkinson's disease; movement disorders and ataxias; learning and memory disorders; eating disorders (e.g., anorexia; bulimia, etc.); obesity; cancers; thymoma; myasthenia gravis; circulatory disorders; prostate cancer; prostatitis; kidney disease/disorders(e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic type 2 diabetes insipidus; cystinuria; polycystic kidney disease); sensorimotor processing and arousal disorders; obsessive-compulsive disorders; testicular cancer; priapism; prostatitis; hernia; endocrine disorders; sexual dysfunction; allergies; depression; psychotic disorders; migraine; reflux; schizophrenia; ulcers; bronchospasm; epilepsy; prostatic hypertrophy; anxiety; rhinitis; angina; and glaucoma. Accordingly, the methods of the present invention may also be useful in the diagnosis and/or treatment of these and other diseases and disorders.

B. Affymetrix GeneChip® Technology

Amino acid sequences were submitted to Affymetrix for the designing and manufacturing of microarray containing oligonucleotides to monitor the expression levels of G protein-coupled receptors (GPCRs) using their GeneChip® Technology. Also present on the microaccray were probes for characterized human brain tissues from Harvard Brain Band or obtained from commercially available sources. RNA samples were amplified, labeled, hybridized to the microarray, and data analyzed according to manufacturer's instructions.

Adipose tissues were monitored for the level of gene expression of each of the GPCRs represented on the microarray. GPCRs were determined to be expressed if the expression index was greater than 100 (based upon and according to manufacturer's instructions). The data was analyzed and had indicated that classification of GPCRs with an expression index greater than 100 was reasonable because a number of known GPCRs had previously been reported to be expressed in neuronal tissues with an expression index greater than 100.

Using the GeneChip, we discovered **hRUP25** to have high levels of expression in adipocytes suggesting that, for example, that **hRUP25** may play a role in lipolysis (*see,* Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition, page 235 (1996). *See* Figure 1. Figure 1 is a plot representing the expression level of **hRUP25** in various tissues. Based upon this data, **hRUP25** is highly expressed by primary adipocytes.

This patent document discloses the identification of nicotinic acid as a ligand and agonist of human, mouse and rat **RUP25**. *See*, Examples *infra*.

EXAMPLE 5

Protocol: Direct Identification of Inverse Agonists and Agonists

A. [^{35}S]GTPγS Assay

Although we have utilized endogenous, constitutively active GPCRs for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. In some embodiments, a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. When such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification of candidate compounds. Thus, in some embodiments it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

1. Membrane Preparation

In some embodiments membranes comprising the constitutively active orphan GPCR/Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists or agonists are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4;

"Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4;

"Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM $MgCl_2$, pH 7.4

b. Procedure

All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. This will then be homogenized using a Brinkman Polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

2. Bradford Protein Assay

Following the homogenization, protein concentration of the membranes will be determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on

the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a Polytron at about 12 x 1,000 rpm for about 5-10 seconds; it was noted that for multiple preparations, the homogenizor should be thoroughly cleaned between homogenization of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contained 800µl Binding Buffer. Thereafter, 10µl of Bradford Protein Standard (1mg/ml) will be added to each tube, and 10µl of membrane Protein will then be added to just one tube (not the blank). Thereafter, 200µl of Bradford Dye Reagent will be added to each tube, followed by vortex of each. After five (5) minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at wavelength 595.

3. Direct Identification Assay

a. Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 µM GDP (final concentration of GDP in each well was 0.1 µM GDP); each well comprising a candidate compound, has a final volume of 200µl consisting of 100µl GDP Buffer (final concentration, 0.1µM GDP), 50µl Membrane Protein in Binding Buffer, and 50µl [^{35}S]GTPγS (0.6 nM) in Binding Buffer (2.5 µl [^{35}S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) will then be diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5µg/well). Thereafter, 100 µl GDP Buffer was added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool will then be used to transfer 5 µl of a candidate compound into such well (*i.e.*, 5µl in total assay volume of 200 µl is a 1:40 ratio such that the final screening concentration of the candidate compound is 10µM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X)

and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 µl of Membrane Protein will be added to each well (a control well comprising membranes without the GPCR Fusion Protein was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50µl of [^{35}S]GTPγS (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will then be stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel manifold and sealed with plate covers. The plates will then be read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer instructions).

B. Cyclic AMP Assay

Another assay approach to directly identified candidate compound was accomplished by utilizing a cyclase-based assay. In addition to direct identification, this assay approach can be utilized as an independent approach to provide confirmation of the results from the [^{35}S]GTPγS approach as set forth above.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was preferably utilized for direct identification of candidate compounds as inverse agonists and agonists to constitutively activated orphan GPCRs in accordance with the following protocol.

Transfected cells were harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization was performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet was then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 x g for 15 minutes at 4°C. The resulting pellet was then stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet was slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer [comprising 2 µCi of tracer ^{125}I-cAMP (100 µl) to 11 ml Detection Buffer] were prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM phospocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 µM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer was then stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature)

were added, preferably, to 96-well plate wells (3µl/well; 12µM final assay concentration), together with 40 µl Membrane Protein (30µg/well) and 50µl of Assay Buffer. This admixture was then incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100µl of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

Example 6

Melanophore Technology

Melanophores are skin cells found in lower vertebrates. They contain pigmented organelles termed melanosomes. Melanophores are able to redistribute these melanosomes along a microtubule network upon G-protein coupled receptor (GPCR) activation. The result of this pigment movement is an apparent lightening or darkening of the cells. In melanophores, the decreased levels of intracellular cAMP that result from activation of a Gi-coupled receptor cause melanosomes to migrate to the center of the cell, resulting in a dramatic lightening in color. If cAMP levels are then raised, following activation of a Gs-coupled receptor, the melanosomes are re-dispersed and the cells appear dark again. The increased levels of diacylglycerol that result from activation of Gq-coupled receptors can also induce this re-dispersion. In addition, the technology is also suited to the study of certain receptor tyrosine kinases. The response of the melanophores takes place within minutes of receptor activation and results in a simple, robust color change. The response can be easily detected using a conventional absorbance microplate reader or a modest video imaging system. Unlike other skin cells, the melanophores derive from the neural crest and appear to express a full complement of signaling proteins. In particular, the cells express an extremely wide range of G-proteins and so are able to functionally express almost all GPCRs.

Melanophores can be utilized to identify compounds, including natural ligands, against GPCRs. This method can be conducted by introducing test cells of a pigment cell line capable of dispersing or aggregating their pigment in response to a specific stimulus and expressing an exogenous clone coding for the GCPR. A stimulant, *e.g.*, melatonin, sets an initial state of pigment disposition wherein the pigment is aggregated within the test cells if activation of the GPCR induces pigment dispersion. However, stimulating the cell with a stimulant to set an initial state of pigment disposition wherein the pigment is dispersed if activation of the GPCR induces pigment aggregation. The test cells are then contacted with chemical compounds, and it is determined whether the pigment disposition in the cells changed from the initial state of pigment disposition. Dispersion of pigments cells due to the candidate compound, including but not limited to a ligand, coupling to the GPCR will appear dark on a petri dish, while aggregation

of pigments cells will appear light.

Materials and methods will be followed according to the disclosure of U.S. Patent Number 5,462,856 and U.S. Patent Number 6,051,386. These patent disclosures are hereby incorporated by reference in their entirety.

Melanophores were transfected by electroporation with plasmids coding for the GPCRs, for example **hRUP25**. Pre-screening of the GPCRs in melanophores was performed in the absence of nicotinic acid following the protocol below to determine the G protein coupling. This pre-screen evidenced that **hRUP25** (Figure 2) is strongly Gi-coupled.

The cells were plated in 96-well plates (one receptor per plate). 48 hours post-transfection, half of the cells on each plate were treated with 10nM melatonin. Melatonin activates an endogenous Gi-coupled receptor in the melanophores and causes them to aggregate their pigment. The remaining half of the cells were transferred to serum-free medium 0.7X L-15 (Gibco). After one hour, the cells in serum-free media remained in a pigment-dispersed state while the melatonin-treated cells were in a pigment-aggregated state. At this point, the cells were treated with a dose response of nicotinic acid (Sigma). If the plated GPCRs bound to nicotinic acid, the melanophores would be expected to undergo a color change in response to the compound. If the receptor were either a Gs or Gq coupled receptor, then the melatonin-aggregated melanophores would undergo pigment dispersion. In contrast, if the receptor was a Gi-coupled receptor, then the pigment-dispersed cells would be expected to undergo a dose-dependent pigment aggregation.

Melanophores transfected with **hRUP25** were treated with nicotinic acid. Upon this treatment, the cells underwent pigment aggregation in a dose-dependent manner. **hRUP25**-expressing cells that were pre-aggregated with melatonin did not disperse upon nicotinic acid treatment, which is consistent with the receptor being a Gi-coupled receptor. *See*, Figure 3 and *infra*.

To confirm and extend these results, melanophores were transfected with a range of **hRUP25** DNA from 0 to 10μg. As controls, melanophores were also transfected with 10μg of α_{2A} Adrenergic receptor (a known Gi-coupled receptor) and salmon sperm DNA (Gibco), as a mock transfection. On day 3, the cells were again incubated for 1 hour in serum-free L-15 medium (Gibco) and remained in a pigment-dispersed state. The cells were then treated with a dose response of nicotinic acid. *See*, Figure 3A. Figure 3A depicts the aggregation response of nicotinic acid at melanophores transfected with various ranges of **hRUP25**. At 10μg of **hRUP25**, the EC_{50} for nicotinic acid is about 54nM. Stated differently, at very low concentrations, nicotinic acid evidences binding to **hRUP25**.

Reference is now made to Figure 3B. In Figure 3B, both the mock transfected and

α_{2A} transfected cells did not respond to nicotinic acid. This data evidences that nicotinic acid binds specifically to the Gi-coupled receptor **hRUP25**.

The data show that the greater the amount of **hRUP25** plasmid DNA transfected, the greater the magnitude of the observed aggregation response. Collectively these data indicate that **hRUP25**: 1) is a Gi-coupled receptor that 2) binds to nicotinic acid.

As set forth herein, nicotinic acid is a ligand for, and agonist of, human, mouse and rat **RUP25**. It is further shown that human, mouse and rat **RUP25** are Gi-coupled. Additionally, human, mouse, and rat **RUP25** can be used in methods described herein to identify antagonists, agonists, inverse agonists, partial agonists, allosteric enhancers, and negative allosteric modulators. As discussed *supra*, methods of modifying nicotinic acid receptor activity in adipocytes using a modulator of the receptor are set forth. Preferably, the modulator is an agonist.

Example 7

Nicotinic Acid Induced-Inositol Phosphates Accumulation in 293 Cells Co-Expressing HRUP and GQΔGI

Figure 4 illustrates the nicotinic acid induced-inositol phosphates (IPs) accumulation in HEK293 cells co-expressing **hRUP25** and the chimeric Gαq-subunit in which the last five amino acids have been replaced with the corresponding amino acids of Gαi (GqΔGi). This construct has been shown to convert the signaling of a Gi-coupled receptor to the Gq pathway (i.e. accumulation of inositol phosphates) in response to receptor activation. Cells transfected with GqΔGi plus either empty plasmid or the constitutively activated α_{2A}AR (α_{2A}K) served as controls for the IP assay which are non-responsive to nicotinic acid.

Example 8

Nicotinic Acid and Nicotine Induced-Inhibition of Forskolin Stimulated CAMP Accumulation in HRUP25-CHO Cell Stable Line #46

Figure 5A is a set of immunofluorescent photomicrographs illustrating the expression of hemaglutinin(HA)-tagged **hRUP25** in a stably transfected line of CHO cells (top; clone #46). No significant labeling is detected in mock stably-transfected CHO cells (Mock). The lower panels identify the nuclear (DAPI) staining of cells in the same field.

Figure 5B illustrates nicotinic acid and nicotine induced-inhibition of forskolin stimulated cAMP accumulation in **hRUP25**-CHO cell stable line #46 (described in preceding paragraph). The EC_{50} for nicotinic acid is 23.6nM and that for nicotine is 9.8μM.

Example 9

hRUP25 AND mRUP25 Inhibit TSHR Induced-cAMP Accumulation Following Activation by Nicotinic Acid

Figure 6 indicates that, in response to nicotinic acid, both **hRUP25** and the mouse ortholog **mRUP25** can inhibit TSHR stimulated cAMP production (in the presence and absence of TSH).

Example 10

hRUP25 and mRUP25 Bind to Nicotinic Acid Specifically and with High Affinity

Figure 7 shows the saturation binding curves of [^{3}H]nicotinic acid ([^{3}H]NA) to membranes prepared from HEK293 cells transiently expressing either **hRUP25** or **mRUP25**. Note the significant binding of [^{3}H]NA relative to either that found in membranes derived from mock transfected cells or in the presence of an excess of non-labeled nicotinic acid (200μM).

Radioligand binding was done as follows. Media was removed from cells grown in culture [either stably or transiently transfected with negative control (empty plasmid) or with the individual receptors **hRUP25**, **mRUP25**, **rRUP25** and cells were scraped and homogenized in buffer containing 15mM HEPES, 5mM EDTA, 5mM EGTA, plus protease inhibitors (leupeptin, PMSF and pepstatin). Membranes were harvested following centrifugation at 30,000 X g, 4°C for 30min. Membranes were then resuspended and re-homogenized in CHAPS binding buffer (50mM Tris-HCl and 0.02% CHAPS, pH 7.4). Aliquots were taken for protein analysis *via* the Bradford protein assay and normalized such that each binding reaction contained the same amount of membrane protein (25-50μg). 50nM [^{3}H]nicotinic acid was added to each sample and either buffer (for total samples) or a desired amount of non-labeled compound (at the same volumes and in the same diluent) was added and the reactions were left at room temperature gently shaking for 1hr. Free ligand was separated from bound ligand *via* rapid filtration onto a filter. Appropriate scintilant was added to each sample and counted in an appropriate scintillation counter. Data was analyzed using Excel and PrismGraph. In some cases radioligand binding was performed using a scintillation proximity assay (SPA) in which case the samples did not require filtration or the addition of scintilant.

Example 11

The Rank Order of Potency of Compounds on hRUP25 Closely Matches That of the Pharmacologically Defined Nicotinic Acid Receptor

Figure 8 is a table comparing the rank order of potency of various compounds on **hRUP25** and the pharmacologically defined nicotinic acid receptor. The potencies at **hRUP25** derived both by a functional analysis measuring the inhibition of forskolin induced cAMP production and competitive radioligand binding assays, closely match the order of potencies of the pharmacologically defined nicotinic acid receptor.

Example 12

Nicotinic Acid and Related Compounds Inhibit Isoproterenol Induced Lipolysis in Rat Epidimal Fat Derived Adipocytes

Figure 9A depicts nicotinic acid and related compounds inhibiting isoproterenol induced lipolysis in rat epidimal fat derived adipocytes at a concentration of 10μM. P-3-T represents 3-tetrazole-5-pyridine.

Figure 9B illustrates a nicotinic acid dose-dependent inhibition of isoproterenol induced-lipolysis in rat epidimal fat derived adipocytes. Note the rightward shift in the dose-response curves with increasing concentrations of nicotinic acid.

Lipolysis assays were done following the isolation of adipocytes from rat or human. The source of fat from rats was the epididymal fat and from humans was either subcutaneous or omental. Cells were isolated following collagenase digestion and floatation. An elevation of intracellular cAMP levels and concomitant activation of lipolysis *via* hormone sensitive lipase was accomplished using isoproterenol, forskolin, 3-isobutyl-1-methyl-xanthine (IBMX) or a combination thereof at concentrations and times determined empirically and depending on the source of tissue. Lipolysis was allowed to continue for the desired time in the presence or absence of drug (*e.g.* nicotinic acid, P-3-T, etc). Data was analyzed using Excel and PrismGraph.

Example 13

Dose-Dependent Inhibition of Isoproterenol Induced-Lipolysis in Human, Subcutaneous-Derived, Primary Adipocytes via Nicotinic Acid and P-3-T

Figure 10 illustrates the ability of both nicotinic acid and the related compound P-3-T (3-tetrazole-5-pyridine) to inhibit isoproterenol induced lipolysis in adipocyte primary cultures derived from human subcutaneous fat in a dose-dependant manner. The EC_{50} value for nicotinic acid and P-3-T were 716nM and 218nM respectively.

Example 14

SUMMARY: hRUP25, mRUP25 and rRUP25.

TABLE C

Disclosed Nicotinic Acid Receptor Sub-Family GPCRs	Expression by Adipocytes or Adipose	Gi-Coupled (Lowers the Level of Intracellular cAMP)	Shown to Inhibit Intracellular Lipolysis	Agonist
hRUP25	yes	yes	yes	nicotinic acid; nicotine; *see* Figure 8
mRUP25	yes	yes	yes	nicotinic acid
rRUP25	yes	yes	yes	nicotinic acid

Example 15

Rodent Diabetes Models

Rodent models of type 2 diabetes associated with obesity and insulin resistance have been developed. Genetic models such as db/db and ob/ob [*see* Diabetes (1982) 31:1-6] in mice and fa/fa in zucker rats have been developed for understanding the pathophysiology of disease and for testing candidate therapeutic compounds [Diabetes (1983) 32:830-838; Annu Rep Sankyo Res Lab (1994) 46:1-57]. The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory are obese, hyperglycemic, hyperinsulinemic and insulin resistant [J Clin Invest (1990) 85:962-967], whereas heterozygotes are lean and normoglycemic. In the db/db model, mice progressively develop insulinopenia with age, a feature commonly observed in late stages of human type 2 diabetes when sugar levels are insufficiently controlled. Since this model resembles that of human type 2 diabetes, the compounds of the present invention are tested for activities including, but not limited to, lowering of plasma glucose and triglycerides. Zucker (fa/fa) rats are severely obese, hyperinsulinemic, and insulin resistant {Coleman, Diabetes (1982) 31:1; E Shafrir in Diabetes Mellitus, H Rifkin and D Porte, Jr, Eds [Elsevier Science Publishing Co, New York, ed. 4, (1990), pp. 299-340]}, and the fa/fa mutation can be the rat equivalent of the murine db mutation [Friedman et al, Cell (1992) 69:217-220; Truett et al, Proc Natl Acad Sci USA (1991) 88:7806]. Tubby (tub/tub) mice are characterized by obesity, moderate insulin resistance and hyperinsulinemia without significant hyperglycemia [Coleman et al, Heredity (1990) 81:424].

The present invention encompasses the use of compounds of the invention for reducing the insulin resistance and hyperglycemia in any or all of the above rodent diabetes

models, in humans with type 2 diabetes or other preferred metabolic-related disorders or disorders of lipid metabolism described previously, or in models based on other mammals. Plasma glucose and insulin levels will be tested, as well as other factors including, but not limited to, plasma free fatty acids and triglycerides.

In Vivo Assay for Anti-Hyperglycemic Activity of Compounds of the Invention

Genetically altered obese diabetic mice (db/db) (male, 7-9 weeks old) are housed (7-9 mice/cage) under standard laboratory conditions at 22°C and 50% relative humidity, and maintained on a diet of Purina rodent chow and water *ad libitum*. Prior to treatment, blood is collected from the tail vein of each animal and blood glucose concentrations are determined using One Touch Basic Glucose Monitor System (Lifescan). Mice that have plasma glucose levels between 250 to 500 mg/dl are used. Each treatment group consists of seven mice that are distributed so that the mean glucose levels are equivalent in each group at the start of the study. The db/db mice are dosed by micro-osmotic pumps, inserted using isoflurane anesthesia, to provide compounds of the invention, saline, or an irrelevant compound to the mice subcutaneously (s.c.). Blood is sampled from the tail vein at intervals thereafter and analyzed for blood glucose concentrations. Significant differences between groups (comparing compounds of the invention to saline-treated) are evaluated using Student t-test.

Example 16

Mouse Atherosclerosis Model

Adiponectin-deficient mice generated through knocking out the adiponectin gene have been shown to be predisposed to atherosclerosis and to be insulin resistant. The mice are also a suitable model for ischemic heart disease [Matsuda, M et al. J Biol Chem (2002) July, and references cited therein, the disclosures of which are incorporated herein by reference in their entirety].

Adiponectin knockout mice are housed (7-9 mice/cage) under standard laboratory conditions at 22°C and 50% relative humidity. The mice are dosed by micro-osmotic pumps, inserted using isoflurane anesthesia, to provide compounds of the invention, saline, or an irrelevant compound to the mice subcutaneously (s.c.). Neointimal thickening and ischemic heart disease are determined for different groups of mice sacrificed at different time intervals. Significant differences between groups (comparing compounds of the invention to saline-treated) are evaluated using Student t-test.

Example 17

***In Vivo* Animal Model For Dyslipidemia and Atherosclerosis**

The utility of the compound of the present invention as a medical agent in the

prophylaxis and treatment of a high total cholesterol/HDL-cholesterol ratio and conditions relating thereto is demonstrated by the activity of the compound in lowering the ratio of total cholesterol to HDL-cholesterol, in elevating HDL-cholesterol, or in protection from atherosclerosis in an *in vivo* pig model. Pigs are used as an animal model because they reflect human physiology, especially lipid metabolism, more closely than most other animal models. An illustrative *in vivo* pig model not intended to be limiting is presented here.

Yorkshire albino pigs (body weight 25.5 ± 4 kg) are fed a saturated fatty acid rich and cholesterol rich (SFA-CHO) diet during 50 days (1 kg chow 35 kg^{-1} pig weight), composed of standard chow supplemented with 2% cholesterol and 20% beef tallow [Royo T et al., *European Journal of Clinical Investigation* (2000) 30:843-52; which disclosure is hereby incorporated by reference in its entirety]. Saturated to unsaturated fatty acid ratio is modified from 0.6 in normal pig chow to 1.12 in the SFA-CHO diet. Animals are divided into two groups, one group (n = 8) fed with the SFA-CHO diet and treated with placebo and one group (n = 8) fed with the SFA-CHO diet and treated with the compound (3.0 mg kg^{-1}). Control animals are fed a standard chow for a period of 50 days. Blood samples are collected at baseline (2 days after the reception of the animals), and 50 days after the initiation of the diet. Blood lipids are analyzed. The animals are sacrificed and necropsied.

Alternatively, the foregoing analysis comprises a plurality of groups each treated with a different dose of the compound. Preferred said doses are selected from the group consisting of: 0.1 mg kg^{-1}, 0.3 mg kg^{-1}, 1.0 mg kg^{-1}, 3.0 mg kg^{-1}, 10 mg kg^{-1}, 30 mg kg^{-1} and 100 mg kg^{-1}. Alternatively, the foregoing analysis is carried out at a plurality of timepoints. Preferred said timepoints are selected from the group consisting of 10 weeks, 20 weeks, 30 weeks, 40 weeks, and 50 weeks.

<u>HDL-Cholesterol</u>

Blood is collected in trisodium citrate (3.8%, 1:10). Plasma is obtained after centrifugation (1200 g 15 min) and immediately processed. Total cholesterol, HDL-cholesterol, and LDL-cholesterol are measured using the automatic analyzer Kodak Ektachem DT System (Eastman Kodak Company, Rochester, NY, USA). Samples with value parameters above the range are diluted with the solution supplied by the manufacturer and then re-analyzed. The total cholesterol/HDL-cholesterol ratio is determined. Comparison is made of the level of HDL-cholesterol between groups. Comparison is made of the total cholesterol/HDL-cholesterol ratio between groups.

Elevation of HDL-cholesterol or reduction of the total cholesterol/HDL-cholesterol ratio on administration of the compound is taken as indicative of the compound having the aforesaid utility.

Atherosclerosis

The thoracic and abdominal aortas are removed intact, opened longitudinally along the ventral surface, and fixed in neutral-buffered formalin after excision of samples from standard sites in the thoracic and abdominal aorta for histological examination and lipid composition and synthesis studies. After fixation, the whole aortas are stained with Sudan IV and pinned out flat, and digital images are obtained with a TV camera connected to a computerized image analysis system (Image Pro Plus; Media Cybernetics, Silver Spring, MD) to determine the percentage of aortic surface involved with atherosclerotic lesions [Gerrity RG et al, *Diabetes* (2001) 50:1654-65; Cornhill JF et al, *Arteriosclerosis, Thrombosis, and Vascular Biology* (1985) 5:415-26; which disclosures are hereby incorporated by reference in their entirety]. Comparison is made between groups of the percentage of aortic surface involved with atherosclerotic lesions.

Reduction of the percentage of aortic surface involved with atherosclerotic lesions on administration of the compound is taken as indicative of the compound having the aforesaid utility.

Example 18

***In Vitro* Biological Activity**

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is used for direct identification of candidate compounds as agonists to hRUP25 in accordance with the following protocol:

Stably transfected CHO cells (clone 46) were harvested from flasks *via* non-enzymatic means. The cells were washed in PBS and resuspended in the manufacturer's Assay Buffer. Live cells were counted using a hemacytometer and Trypan blue exclusion, and the cell concentration was adjusted to $2x10^6$ cells/ml. cAMP standards and Detection Buffer (comprising 2 μCi of tracer [^{125}I]-cAMP (100 μl) to 11 ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. Candidate compounds identified as per above (if frozen, thawed at room temperature) were added to their respective wells (preferably wells of a 96-well plate) at increasing concentrations (3μl/well; 12μM final assay concentration). To these wells, 100,000 cells in 50μl of Assay Buffer were added and the mixture was then incubated for 30 minutes at room temperature, with gentle shaking. Following the incubation, 100μl of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

The biological activities for several representative compounds using the above mentioned assay are shown in the table below:

Compound No.	RUP25 (EC_{50}) (μM)
48	4.3
63	7.9

The majority of the compounds of the Examples showed activities of at least about 60 μM.

Example 19

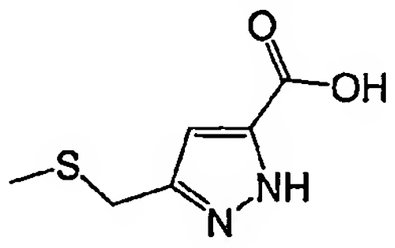
General Synthesis of compounds of Formula (I) - Pyrazole Formation:

To a solution of NaOEt in EtOH (either prepared by the addition of Na or commereically available NaOEt; 17.4 mmol; EtOH 20 mL), is added a ketone (15 mmol) and diethyl oxalate (2.2 g, 15 mmol) at room temperature. The reaction is heated to 75 °C and maintained at the same temperature for two hours. The reaction is cooled to room temperature and treated with a solution of $NH_2NH_2 \cdot HCl$ (1.57 g 15 mmol) in H_2O (3 mL). The subsequent reaction mixture is allowed to stir at 75 °C for two hours. The reaction is cooled to room temperature and concentrated under vacuum. The resulting residue is dissolved in 2.5M NaOH (10 mL) and heated to 95 °C. After stirring for two hours, the reaction is cooled to room temperature and washed with ether (5 mL). The aqueous layer is neutralized (pH = 6.5) with 2M HCl at 0 °C. The reaction is stirred at 0 °C for one hour and the product is filtered. The solid is washed with H_2O (10 mL) and dried under vacuum to afford the desired compound. The product if not a solid can be purified via methods known in the art, for example, by column chromatography or HPLC.

Utilizing the above procedure with 2-hexanone (1.5 g, 15 mmol) gave the desired product, as the carboxylic acid after hydrolysis, 1.69 g (67% yield, unoptimized).

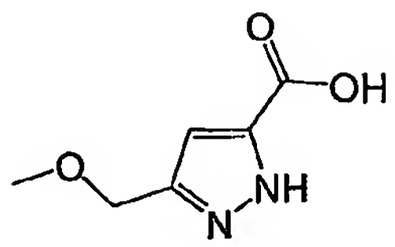
Representative compounds of the present invention:

Compound 48: 5-Methylsulfanylmethyl-2*H*-pyrazole-3-carboxylic acid.



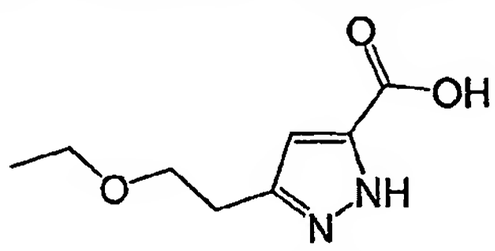
Compound 48 was prepared using a similar method as described above; LCMS: 517.4 $(3M+H)^+$, 345.2 $(2M+H)^+$, 173.1 $(MH)^+$, 154.9, 125.1 and 107.0. NMR (400MHz, CD_3OD, ppm): 6.62 (1H, s), 3.63 (2H, s) and 3.3 (3H, s).

Compound 63: 5-Methoxymethyl-2*H*-pyrazole-3-carboxylic acid.



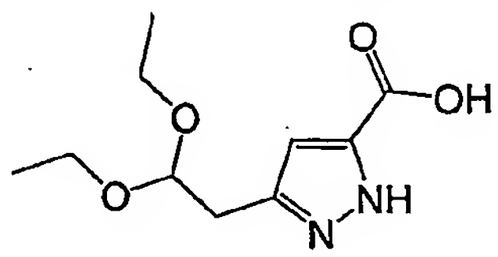
Compound 63 was prepared using a similar method as described above; LCMS: 469.3 $(3M+H)^+$, 313.2 $(2M+H)^+$, 157.0 $(MH)^+$, 139.0, 125.1 and 107.1. NMR (400MHz, $DMSOd_6$, ppm): 13.2 (1H, br. s), 6.75 (1H, s), 4.45 (2H, s) and 3.3 (3H, s).

Compound 64: 5-(2-Ethoxy-ethyl)-2*H*-pyrazole-3-carboxylic acid.



Compound 64 was prepared using a similar method as described above; LCMS: 553.5 $(3M+H)^+$, 369.2 $(2M+H)^+$, 185.0 $(MH)^+$, 167.1 and 121.2. NMR (400MHz, $DMSOd_6$, ppm): 13.1 (1H, br. s), 6.6 (1H, s), 3.68 (2H, t, *J*= 8Hz), 3.5 (2H, q, *J*= 8Hz), 2.88 (2H, t, *J*= 8Hz) and 1.15 (3H, t, *J*= 8Hz).

Compound 65: 5-(2,2-Diethoxy-ethyl)-2*H*-pyrazole-3-carboxylic acid.



Compound 65 was prepared using a similar method as described above; LCMS: 685.5 $(3M+H)^+$, 457.2 $(2M+H)^+$, 229.2 $(MH)^+$, 183.0 and 137.0. NMR (400MHz, $DMSOd_6$, ppm): 13 (1H, br. s), 6.55 (1H, s), 4.7 (1H, t, *J*= 4Hz), 3.6 and 3.58 (2H, qq, *J*= 8Hz), 3.44 and 3.42 (2H, qq, *J*= 8Hz), 2.86 (2H, d, *J*= 8Hz) and 1.05 (6H, t, *J*= 8Hz).

Example 20

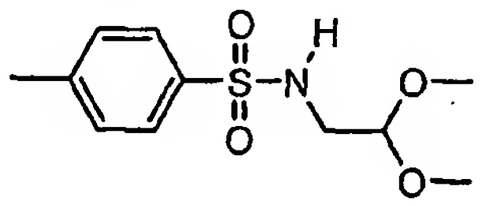
General Synthesis of compounds of Formula (I) - Reductive amination:

To a 20 mL vial with stirring bar is added 5-formyl-1H-pyrazole-3-carboxylic acid ethyl ester (1.19 mmol) and 1,2-dichloroethane (3 mL). An amine (1.19 mmol) is added, followed by sodium triacetoxyborohydride (2.37 mmol). The vial is capped with a septum flushed with N_2, and stirred overnight at room temperature. The mixture is added to $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts are dried (Na_2SO_4), filtered, and concentrated. The crude product is purified using preparatory-HPLC or other purification method known in the art to provide compounds of Formula (I), where R_2 is not H. The purified product can be hydrolysis, for example, using a manner as described

above in Example 19, to give compounds of Formula (I), where R_2 is H.

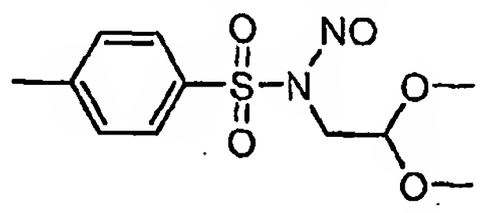
The intermediate 5-formyl-1H-pyrazole-3-carboxylic acid ethyl ester was prepared in the following manner:

Step A: Synthesis of N-(2,2-Dimethoxy-ethyl)-4-methyl-benzenesulfonamide.



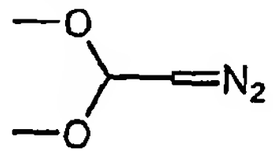
To 350 mL of dry Et_2O was added p-toluenesulfonyl chloride (73.4 g, 385 mmol). Without cooling, a mixture of 2,2-dimethoxy-ethylamine (36.8 g, 350 mmol) and triethylamine (53.7 mL, 385 mmol) was added dropwise to the first solution at a rate sufficient to give a gentle reflux. After stirring 15 h, the reaction was washed with $NaHCO_3$, and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated providing 95.0 g (95%) of N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide.

Step B: Synthesis of N-(2,2-dimethoxyethyl)-N-nitroso-4-tosylamide.



Without further purification, N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfon-amide (95 g, 366 mmol) was taken up in dry Et_2O (350 mL) and treated with HOAc (140 mL), and Ac_2O (140 mL), cooled to 0 °C and stirred. In one portion, $NaNO_2$ (48.3 g, 700 mmol) was added, and the reaction was stirred 2 h at 0 °C, and then 15 h at rt. Saturated $NaHCO_3$ (350 mL) was added, followed by solid $NaHCO_3$ until CO_2 bubbling stopped. The organic layer was separated, and the aqueous portion was extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with $NaHCO_3$ (2 x 50 mL), dried (Na_2SO_4), filtered, and concentrated providing 36.4 g (34%) of N-(2,2-dimethoxyethyl)-N-nitroso-4-tosylamide.

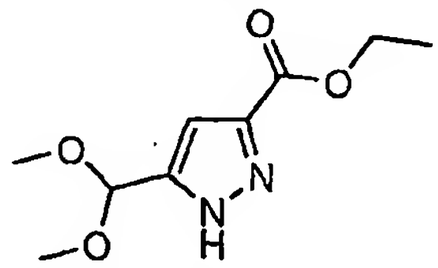
Step C: Synthesis of 2-Diazo-1,1-dimethoxy-ethane.



To a mixture of MeOH (140 mL), H_2O (70 mL), and Et_2O (28 mL) was added KOH (21.1 g, 377 mmol). After the KOH dissolved, the mixture was stirred vigorously at 0 °C. Portionwise, N-(2,2-dimethoxyethyl)-N-nitroso-4-tosylamide (36.4 g, 126 mmol) was added over 15 min., and stirred 2 h at 0 °C. Ether (70 mL) and 2 M KOH (70 mL) were added, and the reaction was stirred 2 h at 0 °C. Further 2 M KOH (70 mL) was added to dissolve any solid, and the Et_2O layer was separated. The aqueous portion was extracted with Et_2O until no more yellow color was seen in the organic phase. The combined organic extracts were washed with 2 M KOH (70 mL), dried (Na_2SO_4), and filtered to provide a solution of 2-diazo-

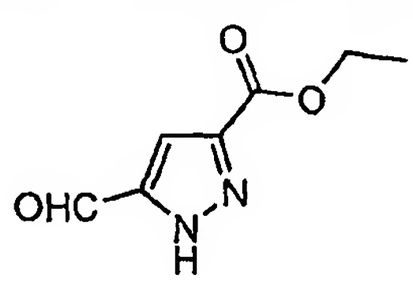
1,1-dimethoxy-ethane in ether.

Step D: Synthesis of 5-Dimethoxymethyl-1H-pyrazole-3-carboxylic acid ethyl ester.



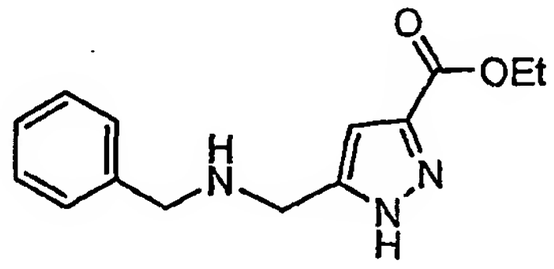
The ether solution of 2-diazo-1,1-dimethoxy-ethane in ether from the previous step was cooled to about -20 °C and treated with propynoic acid ethyl ester (12.8 mL, 126 mmol). The reaction was stirred for 2 h at 0 °C, quenched with AcOH (1.8 mL), and concentrated to afford ~27.4 g of 5-dimethoxymethyl-1H-pyrazole-3-carboxylic acid ethyl ester.

Step E: Synthesis of 5-formyl-1H-pyrazole-3-carboxylic acid ethyl ester.



Amberlyst-15 (19 g) was added to a solution of crude 5-dimethoxymethyl-1H-pyrazole-3-carboxylic acid ethyl ester dissolved in acetone (142 mL) and H_2O (66 mL). After stirring 2 h at rt, the Amberlyst was filtered from the solution, and the filtrate was extracted with EtOAc (2 x 100 mL) and concentrated. The concentrate was suspended in benzene (30 mL) and hexane (120 mL), and stirred 2 h at rt. The precipitate was filtered, washed with 9:1 hexanes/benzene, and air-dried providing 5.29 g [25% from N-(2,2-dimethoxyethyl)-N-nitroso-4-tosylamide] of 5-dimethoxymethyl-1H-pyrazole-3-carboxylic acid ethyl ester: LC-MS *m/z* 167 (M-1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (bs, 1 H), 7.34 (bs, 1 H), 4.37 (m, 2 H), 1.36 (t, J = 7.06 Hz, 3 H).

Compound 62: 5-(Benzylamino-methyl)-1H-pyrazole-3-carboxylic acid ethyl ester.



To a 20 mL vial with stirring bar was added 5-formyl-1H-pyrazole-3-carboxylic acid ethyl ester (0.20 g, 1.19 mmol) and 1,2-dichloroethane (3 mL). Benzylamine (0.130 mL, 1.19 mmol) was added, followed by sodium triacetoxyborohydride (0.504 g, 2.37 mmol). The vial was capped with a septum flushed with N_2, and stirred overnight at room temperature. The mixture was added to $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified using preparatory-HPLC providing 0.254 g (87 %) of 5-(benzylamino-

methyl)-1H-pyrazole-3-carboxylic acid ethyl ester: LC-MS *m/z* 260 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1 H), 7.60-7.31 (m, 5 H), 6.87 (s, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 4.11 (m, 4 H), 1.21 (t, J = 7.3 Hz, 3 H).

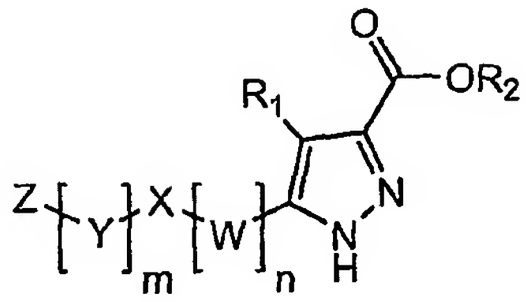
Throughout this application, various publications, patents and published patent applications are cited. The disclosures of these publications, patents and published patent applications referenced in this application are hereby incorporated by reference in their entirety into the present disclosure. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

CLAIMS

What we claim is:

1. A compound of Formula (I):



(I)

wherein:

W and Y are independently a straight or branched chain C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl or C_{1-4} alkoxy;

X is $-NR_3C(O)-$, $-C(O)NR_3$, $-NR_3S(O)_2-$, $-S(O)_2NR_3-$, $-NR_3C(O)NR_4-$, $-NR_3C(O)O-$, $-OC(O)NR_3-$, $-NR_3-$, $-C(O)-$, $-CH(OH)-$, $-C(NH)-$, $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

R_3 and R_4 are independently H, C_{1-4} alkyl, phenyl or heteroaryl, wherein each of said alkyl, phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

Z is H, halogen, phenyl or heteroaryl, wherein said phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxy, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

R_1 is H, hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R_2 is H or C_{1-8} alkyl and

"n" and "m" are each independently 0 or 1; or

a pharmaceutically acceptable salt, solvate or hydrate thereof;

provided that:

i) when both R_1 and R_2 are H then $-[W]_n$-X-$[Y]_m$-Z together is not CO_2H, $C(O)$-C_6H_4-*p*-O-C_8H_{17}, OCH_2CH_3, OH, $CH_2CH_2CH_2CH_2CO_2H$, $CH_2CH_2CH_2CO_2H$, CH_2CO_2H and $CH_2CH_2CO_2H$;

ii) when R_1 is CH_3 and R_2 is H then $-[W]_n$-X-$[Y]_m$-Z together is not CH_2CO_2H, $C(O)CH{=}CH\ C_6H_5$, $C(O)C_6H_4$-*p*-OCH_3, CO_2H, $C(O)CH_3$, $C(O)C_6H_4$-*o*-CH_3, $C(O)C_6H_4$-*o*-Br, $C(O)C_6H_4$-*o*-Cl, and $C(O)C_6H_5$;

iii) when R_1 is Br and R_2 is H then $-[W]_n$-X-$[Y]_m$-Z together is not CO_2H;

iv) when R_1 is OH and R_2 is H then $-[W]_n$-X-$[Y]_m$-Z together is not CO_2H;

v) when R_1 is H and R_2 is CH_3 then $-[W]_n$-X-$[Y]_m$-Z together is not 2,6-dichloro-4-trifluoromethylphenoxy, $C(O)NH$-C_6H_4-*p*-OCH_2CH_3, $NHC(O)CH(CH_3)_2$, SCH_3, $C(O)$-C_6H_4-*p*-O-C_8H_{17}, SCH_2CH_3, $C(O)NHC_6H_5$, $CH(OCH_3)_2$, $CH_2OC(O)CH_3$, CO_2H, CO_2CH_3, $C(O)C_6H_4$-*p*-NO_2, $C(O)C_6H_5$, $CH_2CH_2CO_2CH_3$, $CH_2CH_2CH_2CH_2CO_2CH_3$, $CH_2CH_2CH_2CO_2CH_3$ and $CH_2CO_2CH_3$;

vi) when R_1 is OH and R_2 is CH_3 then $-[W]_n$-X-$[Y]_m$-Z together is not $CH_2OCH_2C_6H_5$, $CH_2OCH(CH_3)_2$ and CH_2OH;

vii) when R_2 is CH_3 then:

R_1 is not CH_3 and $-[W]_n$-X-$[Y]_m$-Z together is not 2,6-dichloro-4-trifluoromethylphenoxy;

R_1 is not I and $-[W]_n$-X-$[Y]_m$-Z together is not $CO_2C(CH_3)_3$;

R_1 is not $C(CH_3)_3$ and $-[W]_n$-X-$[Y]_m$-Z together is not formyl;

R_1 is not Br and $-[W]_n$-X-$[Y]_m$-Z together is not CO_2CH_3; and

R_1 is not $CH_2CH_2CH_2CH_3$ and $-[W]_n$-X-$[Y]_m$-Z together is not formyl;

viii) when R_1 is H and R_2 is CH_2CH_3 then $-[W]_n$-X-$[Y]_m$-Z together is not $CH_2SCH_2CH_3$, $OCH_2CH_2CH{=}CH_2$, $CH_2CH_2CH_2OH$, CH_2CH_2CHO, $CO_2CH_2CH_3$, OCH_3, $C(O)CH_2Br$, $CO_2C_8H_{17}$, formyl, OH, $CH_2N(CH_2CH_2Cl)_2$, $CH(CH_3)OC(O)CH_3$, CH_2OH, $CH_2OC(O)CH_3$, $C(O)CH_3$, $C(O)C_6H_5$ and $C(O)NHCH_2CO_2CH_2CH_3$.

ix) when R_1 is CH_3 and R_2 is CH_2CH_3 then $-[W]_n$-X-$[Y]_m$-Z together is not $CH(OH)C_6H_4$-*p*-$N(CH_3)_2$, $C(O)CH_2C(O)CH_3$, $CO_2CH_2C_6H_5$, CO_2CH_3, $C(O)CH_2CH_2CH_3$, $C(O)CH_3$, $C(O)C_6H_4$-*p*-OCH_3, $C(O)C_6H_4$-*o*-Br, $C(O)C_6H_4$-*p*-Cl, $C(O)C_6H_4$-*o*-Cl, $C(O)CH_2C_6H_5$ and $C(O)C_6H_5$;

x) when R_2 is CH_2CH_3 then:

R_1 is not I and $-[W]_n$-X-$[Y]_m$-Z together is not $CO_2CH_2CH_3$;

R_1 is not CF_3 and $-[W]_n$-X-$[Y]_m$-Z together is not $CO_2CH_2CH_3$; and

R_1 is not Br and $-[W]_n$-X-$[Y]_m$-Z together is not $CO_2CH_2CH_3$;

xi) when R_1 is OH and R_2 is CH_2CH_3 then $-[W]_n$-X-$[Y]_m$-Z together is not $C(O)C_6H_5$, $C(O)NH_2$ and $CO_2CH_2CH_3$;

xii) when R_1 is H and R_2 is $C(CH_3)_3$ then $-[W]_n$-X-$[Y]_m$-Z together is not $CO_2C(CH_3)_3$, $C(O)NHC(O)CH_3$ and $C(O)NH_2$;

xiii) when R_1 is OH and R_2 is $CH_2CH_2CH_2CH_3$ then $-[W]_n$-X-$[Y]_m$-Z together is not $C(O)C_6H_5$; and

xiv) when X is $-NR_3-$ then "n" is 1.

2. The compound according to claim 1 wherein "n" is 0.

3. The compound according to claim 1 wherein "n" is 1.

4. The compound according to any one of claims 1 to 3 wherein "m" is 0.

5. The compound according to any one of claims 1 to 3 wherein "m" is 1.

6. The compound according to any one of claims 1, 3, 4 and 5 wherein W is the straight or branched C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

7. The compound according to claim 6 wherein W is $-CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

8. The compound according to claim 7 wherein W is $-CH(CH_3)-$ optionally substituted with halogen, hydroxyl or C_{1-4} alkoxy.

9. The compound according to claim 7 wherein W is $-C(CH_3)_2-$.

10. The compound according to claim 6 wherein W is $-CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

11. The compound according to claim 10 wherein W is $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

12. The compound according to claim 10 wherein W is $-C(CH_3)_2CH_2-$ or $-CH_2C(CH_3)_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

13. The compound according to claim 10 wherein W is $-CH(OCH_3)CH_2-$ or $-CH_2CH(OCH_3)-$ optionally substituted with halogen, hydroxyl or C_{1-4} alkyl.

14. The compound according to claim 6 wherein W is $-CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

15. The compound according to claim 6 wherein W is $-CH_2CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

16. The compound according to claim 6 wherein W is -CH=CH- optionally substituted with C_{1-4} alkyl or C_{1-4} alkoxy.

17. The compound according to claim 6 wherein W is $-C\equiv C-$.

18. The compound according to claim 6 wherein W is -C(O)-.

19. The compound according to claim 6 wherein W is $-CH_2C(O)-$ or $-C(O)CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

20. The compound according to claim 19 wherein W is $-CH(CH_3)C(O)-$ or $-C(O)CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

21. The compound according to claim 19 wherein W is $-C(CH_3)_2C(O)-$ or $-C(O)C(CH_3)_2-$.

22. The compound according to claim 6 wherein W is $-CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

23. The compound according to claim 22 wherein W is $-C(CH_3)_2CH_2C(O)-$ or $-C(O)CH_2C(CH_3)_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

24. The compound according to claim 6 wherein W is $-CH_2C(O)CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

25. The compound according to claim 6 wherein W is $-CH_2CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

26. The compound according to claim 6 wherein W is $-CH(CH_3)CH_2CH_2C(O)-$ or $-C(O)CH_2CH_2CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

27. The compound according to claim 6 wherein W is $-CH_2CH_2C(O)CH_2-$ or $-CH_2C(O)CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

28. The compound according to claim 6 wherein W is $-CH=CHC(O)-$ or $-C(O)CH=CH-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

29. The compound according to claim 6 wherein W is $-C(CH_3)=CHC(O)-$ or $-C(O)CH=C(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

30. The compound according to any one of claims 1, 2, 3 and 5 to 28 wherein Y is the straight or branched chain C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

31. The compound according to claim 30 wherein Y is $-CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

32. The compound according to claim 31 wherein Y is $-CH(CH_3)-$ optionally substituted

with halogen, hydroxyl or C_{1-4} alkoxy.

33. The compound according to claim 31 wherein Y is $-C(CH_3)_2-$.

34. The compound according to claim 30 wherein Y is $-CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

35. The compound according to claim 34 wherein Y is $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

36. The compound according to claim 34 wherein Y is $-C(CH_3)_2CH_2-$ or $-CH_2C(CH_3)_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

37. The compound according to claim 34 wherein Y is $-CH(OCH_3)CH_2-$ or $-CH_2CH(OCH_3)-$ optionally substituted with halogen, hydroxyl or C_{1-4} alkyl.

38. The compound according to claim 30 wherein Y is $-CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

39. The compound according to claim 30 wherein Y is $-CH_2CH_2CH_2CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

40. The compound according to claim 30 wherein Y is -CH=CH- optionally substituted with C_{1-4} alkyl or C_{1-4} alkoxy.

41. The compound according to claim 30 wherein Y is $-C\equiv C-$.

42. The compound according to claim 30 wherein Y is $-C\equiv CCH_2-$ or $-CH_2C\equiv C-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

43. The compound according to claim 30 wherein Y is -C(O)-.

44. The compound according to claim 30 wherein Y is $-CH_2C(O)-$ or $-C(O)CH_2-$ optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

45. The compound according to claim 44 wherein Y is -$CH(CH_3)C(O)$- or –$C(O)CH(CH_3)$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

46. The compound according to claim 44 wherein Y is -$C(CH_3)_2C(O)$- or -$C(O)C(CH_3)_2$-.

47. The compound according to claim 30 wherein Y is -$CH_2CH_2C(O)$- or -$C(O)CH_2CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

48. The compound according to claim 47 wherein Y is -$C(CH_3)_2CH_2C(O)$- or –$C(O)CH_2C(CH_3)_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

49. The compound according to claim 30 wherein Y is -$CH_2C(O)CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

50. The compound according to claim 30 wherein Y is -$CH_2CH_2CH_2C(O)$- or -$C(O)CH_2CH_2CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

51. The compound according to claim 30 wherein Y is -$CH(CH_3)CH_2CH_2C(O)$- or -$C(O)CH_2CH_2CH(CH_3)$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

52. The compound according to claim 30 wherein Y is -$CH_2CH_2C(O)CH_2$- or -$CH_2C(O)CH_2CH_2$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

53. The compound according to claim 30 wherein Y is -CH=CHC(O)- or -C(O)CH=CH- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

54. The compound according to claim 30 wherein Y is -$C(CH_3)$=CHC(O)- or -C(O)CH=$C(CH_3)$- optionally substituted with halogen, hydroxyl, C_{1-4} alkyl or C_{1-4} alkoxy.

55. The compound according to any one of claims 1 to 54 wherein X is $-NR_3C(O)-$.

56. The compound according to any one of claims 1 to 54 wherein X is $-C(O)NR_3-$.

57. The compound according to any one of claims 1 to 54 wherein X is $-NR_3S(O)_2-$.

58. The compound according to any one of claims 1 to 54 wherein X is $-S(O)_2NR_3-$.

59. The compound according to any one of claims 1 to 54 wherein X is $-NR_3C(O)NR_4-$.

60. The compound according to any one of claims 1 to 54 wherein X is $-NR_3C(O)O-$.

61. The compound according to any one of claims 1 to 54 wherein X is $-OC(O)NR_3-$.

62. The compound according to any one of claims 1 to 54 wherein X is $-NR_3-$.

63. The compound according to any one of claims 55 to 62 wherein R_3 is H or CH_3.

64. The compound according to claim 59 wherein R_4 is H or CH_3.

65. The compound according to any one of claims 1 to 54 wherein X is -C(O)-.

66. The compound according to any one of claims 1 to 54 wherein X is -CH(OH)-.

67. The compound according to any one of claims 1 to 54 wherein X is -C(NH)-.

68. The compound according to any one of claims 1 to 54 wherein X is -O-.

69. The compound according to any one of claims 1 to 54 wherein X is -S-.

70. The compound according to any one of claims 1 to 54 wherein X is -S(O)-.

71. The compound according to any one of claims 1 to 54 wherein X is $-S(O)_2-$.

72. The compound according to any one of claims 1 to 71 wherein Z is H.

73. The compound according to any one of claims 1 to 71 wherein Z is halogen.

74. The compound according to any one of claims 1 to 71 wherein Z is phenyl.

75. The compound according to claim 74 wherein the phenyl is optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, C_{1-4} haloalkyl, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl.

76. The compound according to claim 75 wherein the phenyl is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, $-CF_3$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$ and $-OCF_3$.

77. The compound according to any one of claims 1 to 71 wherein Z is heteroaryl.

78. The compound according to claim 77 wherein the heteroaryl is optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, C_{1-4} haloalkyl, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl.

79. The compound according to claim 78 wherein the phenyl is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, $-CF_3$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$ and $-OCF_3$.

80. The compound according to any one of claims 1 to 79 wherein R_1 is H.

81. The compound according to any one of claims 1 to 79 wherein R_1 is hydroxyl.

82. The compound according to any one of claims 1 to 78 wherein R_1 is halogen.

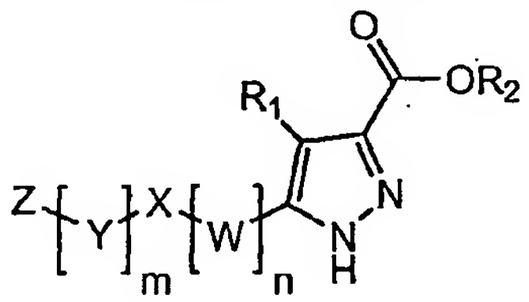
83. The compound according to any one of claims 1 to 78 wherein R_1 is C_{1-4} alkyl.

84. The compound according to any one of claims 1 to 78 wherein R_1 is C_{1-4} haloalkyl.

85. The compound according to any one of claims 1 to 84 wherein R_2 is H.

86. The compound according to any one of claims 1 to 84 wherein R_2 is C_{1-8} alkyl.

87. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with at least one compound according to Formula (I):



(I)

wherein:

W and Y are independently a straight or branched chain C_{1-5} alkylene group optionally containing one double bond, one triple bond or carbonyl, wherein said C_{1-5} alkylene group is optionally substituted with halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} haloalkyl or C_{1-4} alkoxy;

X is $-NR_3C(O)-$, $-C(O)NR_3$, $-NR_3S(O)_2-$, $-S(O)_2NR_3-$, $-NR_3C(O)NR_4-$, $-NR_3C(O)O-$, $-OC(O)NR_3-$, $-NR_3-$, $-C(O)-$, $-CH(OH)-$, $-C(NH)-$, $-O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

R_3 and R_4 are independently H, C_{1-4} alkyl, phenyl or heteroaryl, wherein each of said alkyl, phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxyl, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

Z is H, halogen, phenyl or heteroaryl, wherein said phenyl and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of halogen, hydroxy, thiol, cyano, nitro, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} haloalkylthio, C_{1-4} haloalkylsulfinyl and C_{1-4} haloalkylsulfonyl;

R_1 is H, hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R_2 is H or C_{1-8} alkyl and
"n" and "m" are each independently 0 or 1; or
a pharmaceutically acceptable salt, solvate or hydrate thereof;
provided that when X is $-NR_3-$ then "n" is 1.

88. The pharmaceutical composition according to claim 87 further comprising one or more agents selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

89. The pharmaceutical composition according to claim 88 wherein the agent is a α-glucosidase inhibitor.

90. The pharmaceutical composition according to claim 89 wherein the α-glucosidase inhibitor is acarbose, voglibose or miglitol.

91. The pharmaceutical composition according to claim 90 wherein the α-glucosidase inhibitor is voglibose.

92. The pharmaceutical composition according to claim 88 wherein the agent is an aldose reductase inhibitor.

93. The pharmaceutical composition according to claim 92 wherein the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil.

94. The pharmaceutical composition according to claim 88 wherein the agent is a biguanide.

95. The pharmaceutical composition according to claim 94 wherein the biguanide is phenformin, metformin or buformin.

96. The pharmaceutical composition according to claim 95 wherein the biguanide is metformin.

97. The pharmaceutical composition according to claim 88 wherein the agent is a HMG-

CoA reductase inhibitor.

98. The pharmaceutical composition according to claim 97 wherein the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

99. The pharmaceutical composition according to claim 88 wherein the agent is a fibrate.

100. The pharmaceutical composition according to claim 99 wherein the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate.

101. The pharmaceutical composition according to claim 88 wherein the agent is an angiotensin converting enzyme inhibitor.

102. The pharmaceutical composition according to claim 101 wherein the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril.

103. The pharmaceutical composition according to claim 88 wherein the agent is an insulin secretion enhancer.

104. The pharmaceutical composition according to claim 103 wherein the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide.

105. The pharmaceutical composition according to claim 88 wherein the agent is a thiazolidinedione.

106. The pharmaceutical composition according to claim 105 wherein the thiazolidinedione is rosiglitazone or pioglitazone.

107. The pharmaceutical composition according to claim 106 wherein the thiazolidinedione is rosiglitazone.

108. The compound according to any one of claims 1 to 86 for use in a method of treatment of the human or animal body by therapy.

109. The compound according to any one of claims 1 to 86 for use in a method of prophylaxis or treatment of a metabolic-related disorder of the human or animal body by therapy.

110. A method for prophylaxis or treatment of a metabolic-related disorder in an individual in need of said prophylaxis or treatment comprising administering to the individual a therapeutically effective amount of a compound according to any one of claims 1 to 86 or a pharmaceutical composition according to any one of claims 87 to 107.

111. A method of modulating a RUP25 receptor in an individual comprising contacting the receptor with a compound according to any one of claims 1 to 86.

112. The method of modulating the RUP25 receptor according to claim 111 wherein the compound is an agonist.

113. The method of modulating the RUP25 receptor according to claim 111 or 112 wherein the modulation of the RUP25 receptor is for prophylaxis or treatment of a metabolic-related disorder in an individual in need of said prophylaxis or treatment.

114. The method according to claim 110 or 113 wherein the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

115. The method according to claim 114 wherein the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

116. The method according to claim 115 wherein the metabolic-related disorder is dyslipidemia.

117. The method according to claim 115 wherein the metabolic-related disorder is atherosclerosis.

118. The method according to claim 115 wherein the metabolic-related disorder is coronary heart disease.

119. The method according to claim 115 wherein the metabolic-related disorder is insulin resistance.

120. The method according to claim 115 wherein the metabolic-related disorder is type 2 diabetes.

121. Use of a compound according to any one of claims 1 to 86 for production of a medicament for use in prophylaxis or treatment of a metabolic-related disorder.

122. The use according to claim 121 further comprising one or more agents selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

123. The use according to claim 122 wherein the agent is a α-glucosidase inhibitor.

124. The use according to claim 123 wherein the α-glucosidase inhibitor is acarbose, voglibose or miglitol.

125. The use according to claim 124 wherein the α-glucosidase inhibitor is voglibose.

126. The use according to claim 122 wherein the agent is an aldose reductase inhibitor.

127. The use according to claim 126 wherein the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil.

128. The use according to claim 122 wherein the agent is a biguanide.

129. The use according to claim 128 wherein the biguanide is phenformin, metformin or buformin.

130. The use according to claim 129 wherein the biguanide is metformin.

131. The use according to claim 122 wherein the agent is a HMG-CoA reductase inhibitor.

132. The use according to claim 131 wherein the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

133. The use according to claim 122 wherein the agent is a fibrate.

134. The use according to claim 133 wherein the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate.

135. The use according to claim 122 wherein the agent is an angiotensin converting enzyme inhibitor.

136. The use according to claim 135 wherein the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril.

137. The use according to claim 122 wherein the agent is an insulin secretion enhancer.

138. The use according to claim 137 wherein the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide.

139. The use according to claim 122 wherein the agent is a thiazolidinedione.

140. The use according to claim 139 wherein the thiazolidinedione is rosiglitazone or pioglitazone.

141. The use according to claim 140 wherein the thiazolidinedione is rosiglitazone.

142. The use according to any one of claims 121 to 141 wherein the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

143. The use according to claim 142 wherein the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

144. The use according to claim 143 wherein the metabolic-related disorder is dyslipidemia.

145. The use according to claim 143 wherein the metabolic-related disorder is atherosclerosis.

146. The use according to claim 143 wherein the metabolic-related disorder is coronary heart disease.

147. The use according to claim 143 wherein the metabolic-related disorder is insulin resistance.

148. The use according to claim 143 wherein the metabolic-related disorder is type 2 diabetes.

149. The method of producing a pharmaceutical composition comprising admixing at least one compound according to any one of claims 1 to 86 and a pharmaceutically acceptable carrier or excipient.

Figure 1

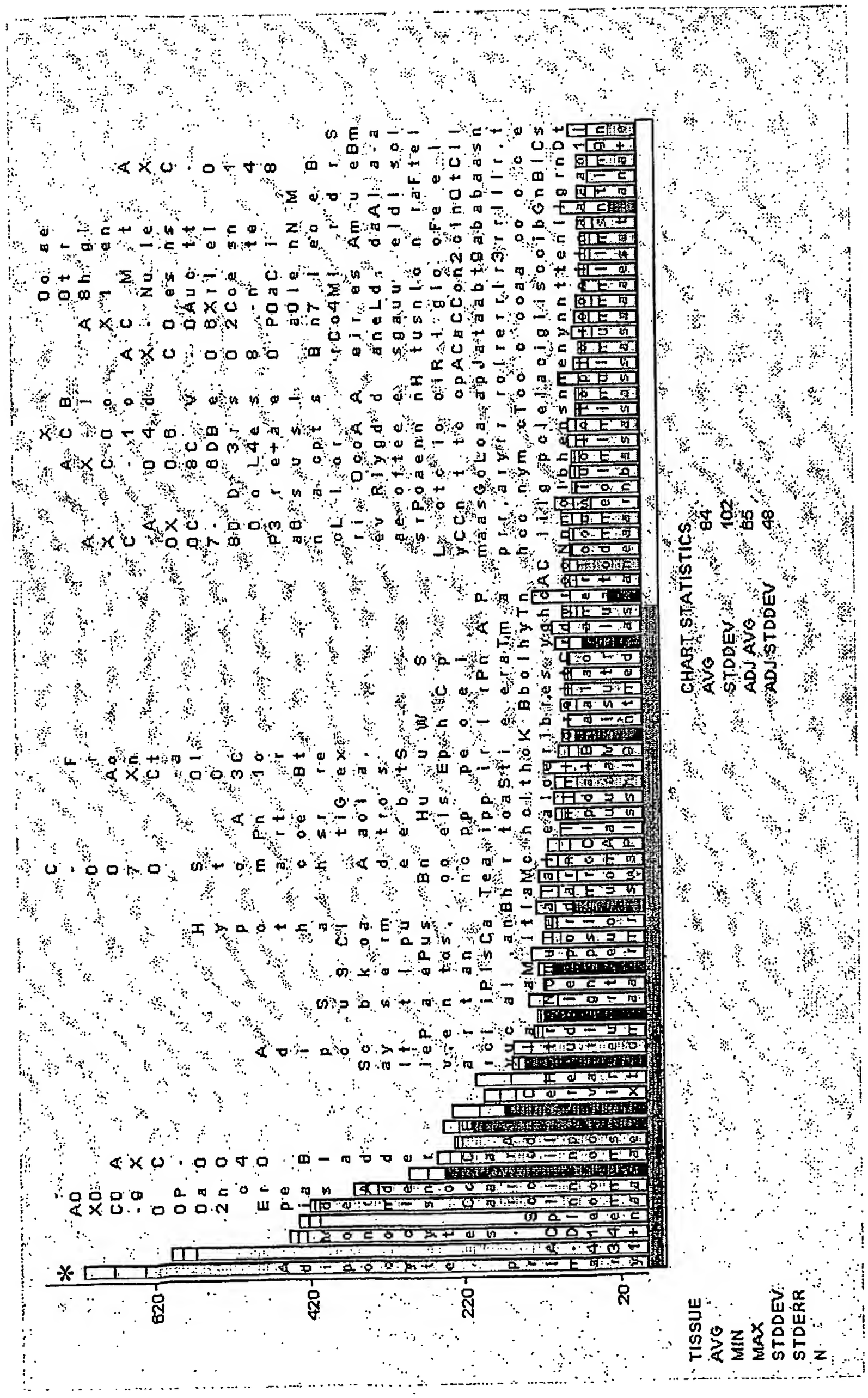
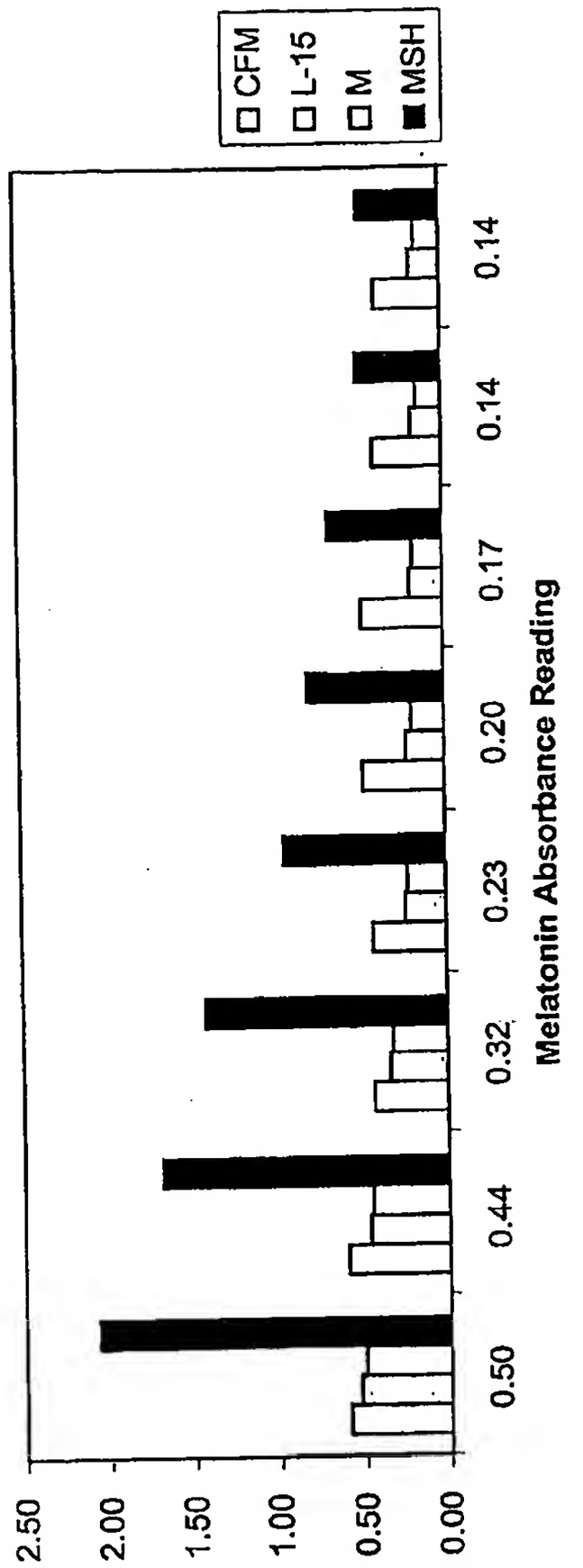


CHART STATISTICS
AVG 84
STDDEV 102
ADJ AVG 85
ADJ STDDEV 48
TISSUE
AVG
MIN
MAX
STDDEV
STDERR
N
620
420
220
20

2/12

Figure 2
RUP25 G_i - coupled constitutive activity in melanophore



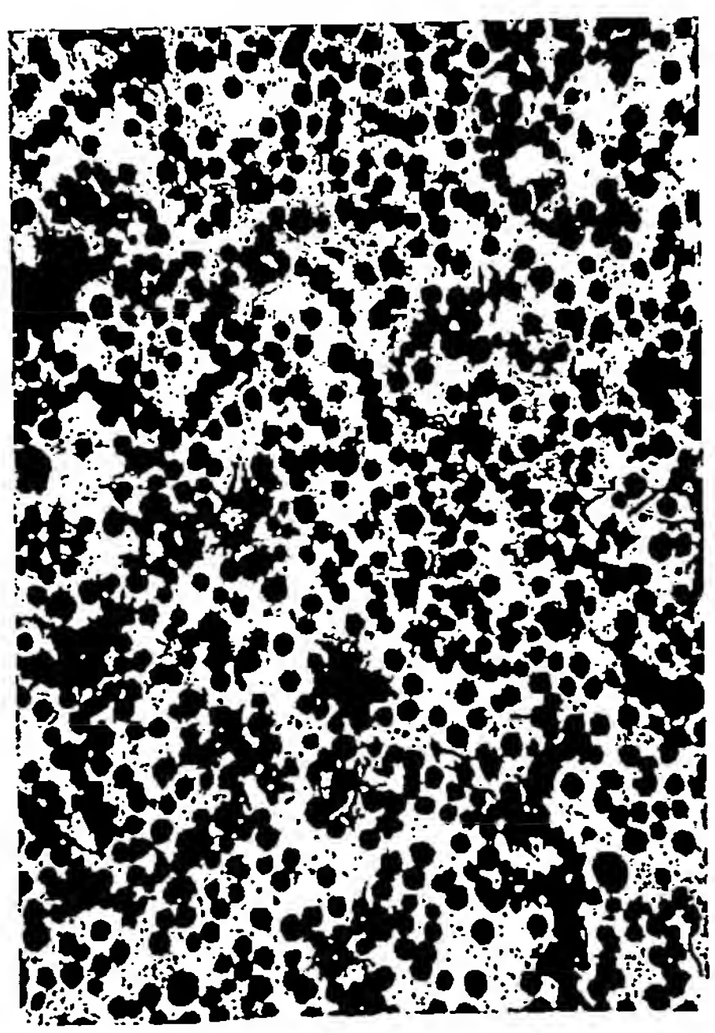


Figure 3A

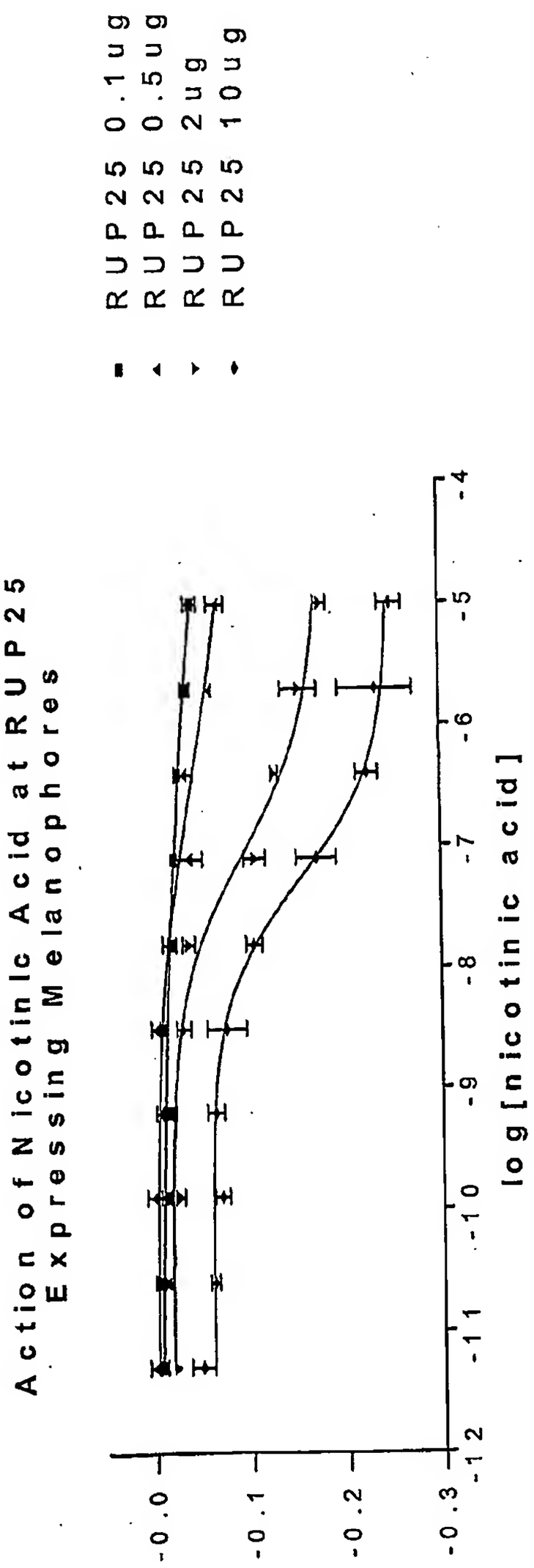


Figure 3B

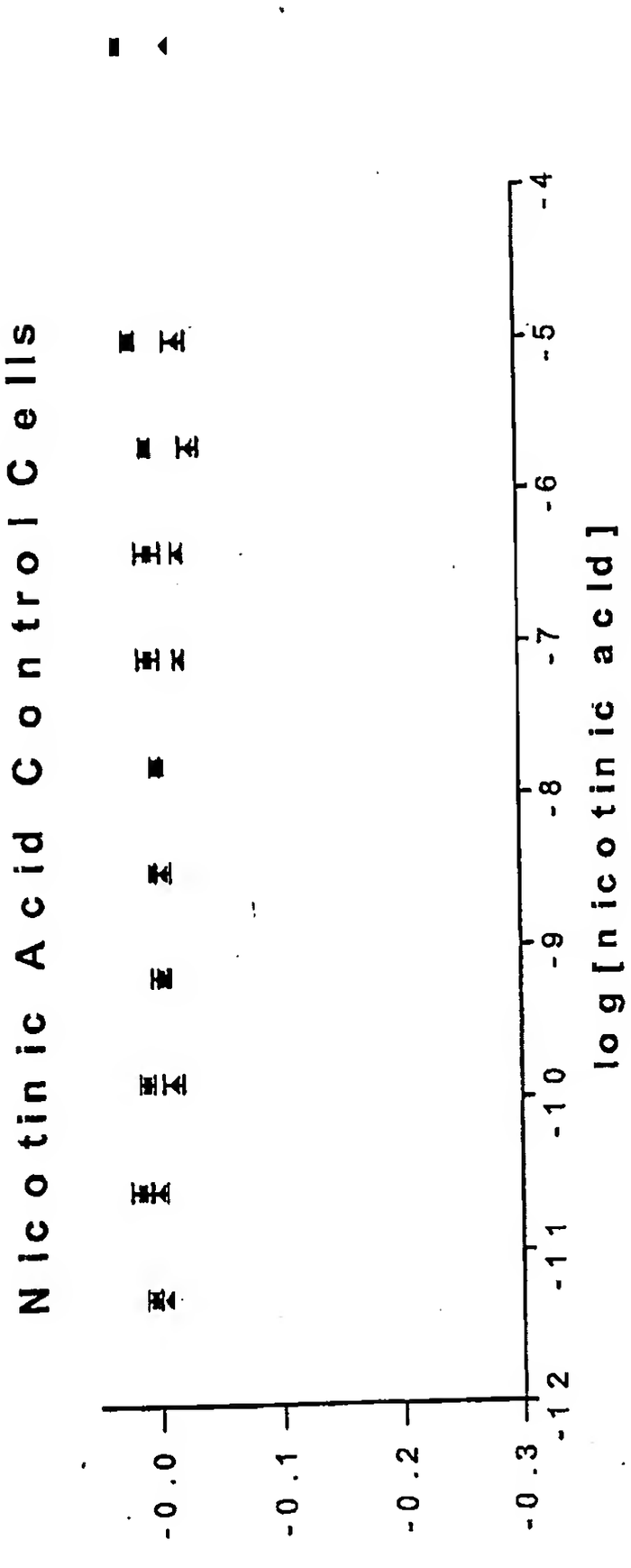


Figure 4

Nicotinic acid induced-IPs accumulation in 293 cells co-expressing hRUP25 and GqΔGi

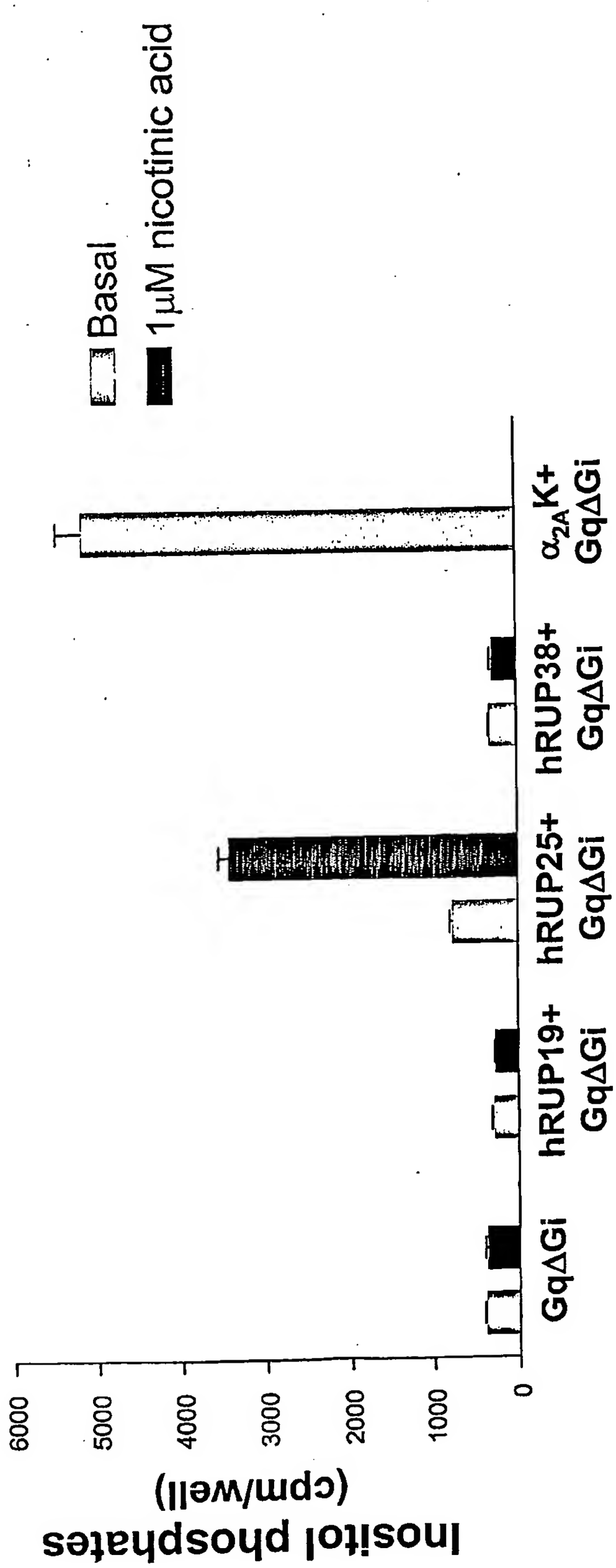


Figure 5A
hRUP25-CHO stable clone identified by anti-HA immunofluorescence staining

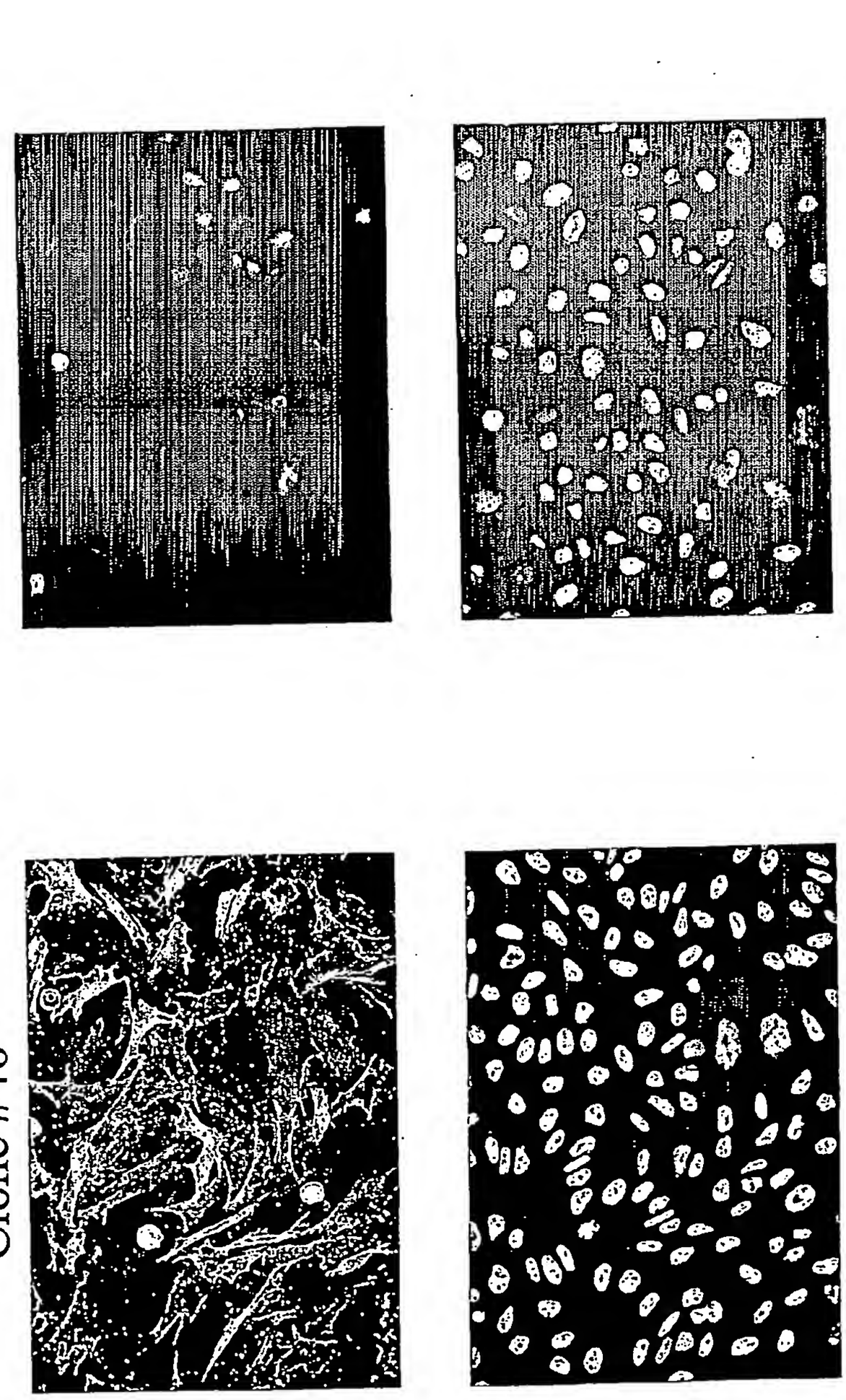
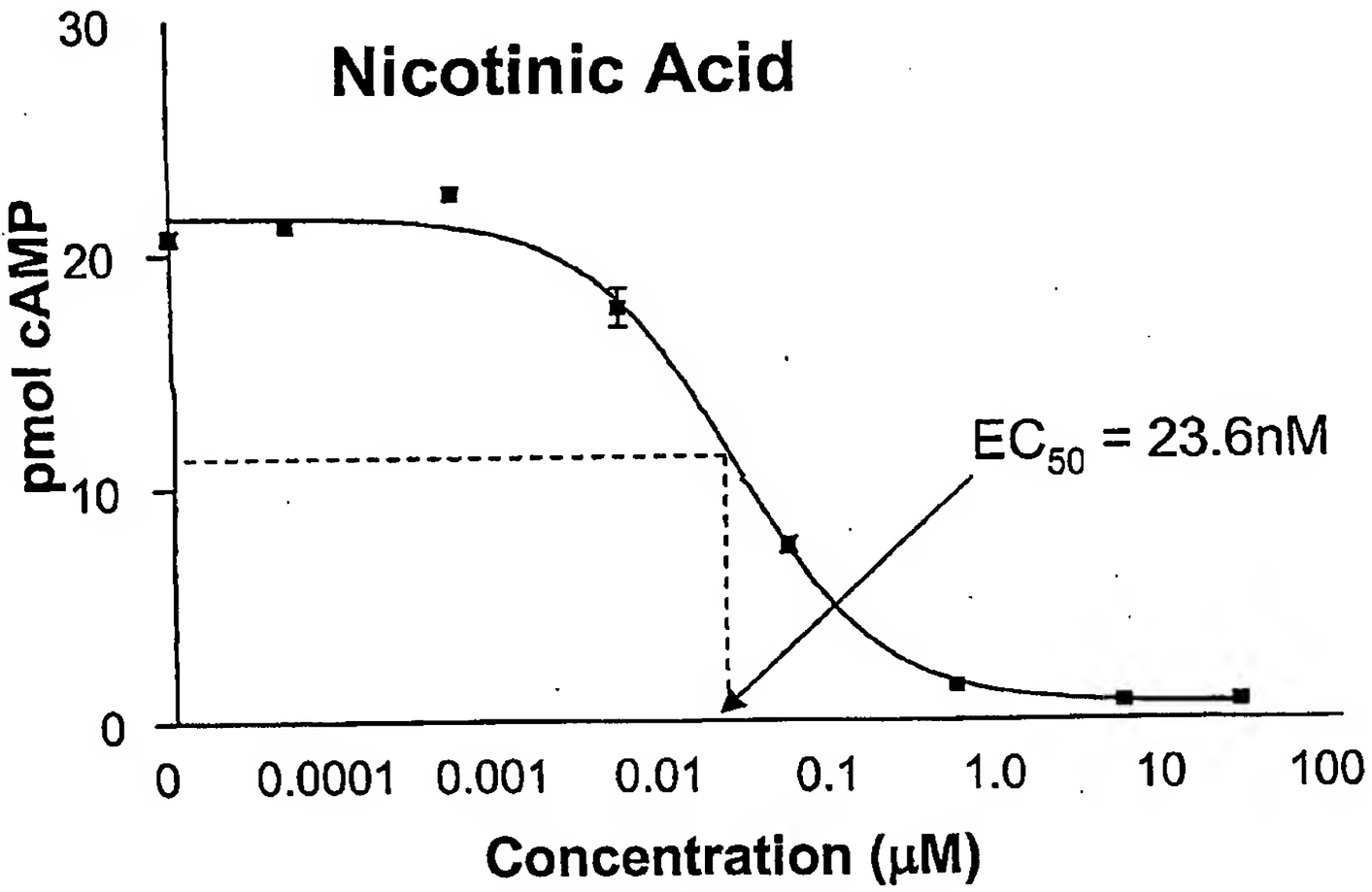


Figure 5B
Nicotinic acid and nicotine induced-inhibition of forskolin stimulated cAMP accumulation in hRUP25-CHO cell stable line #46



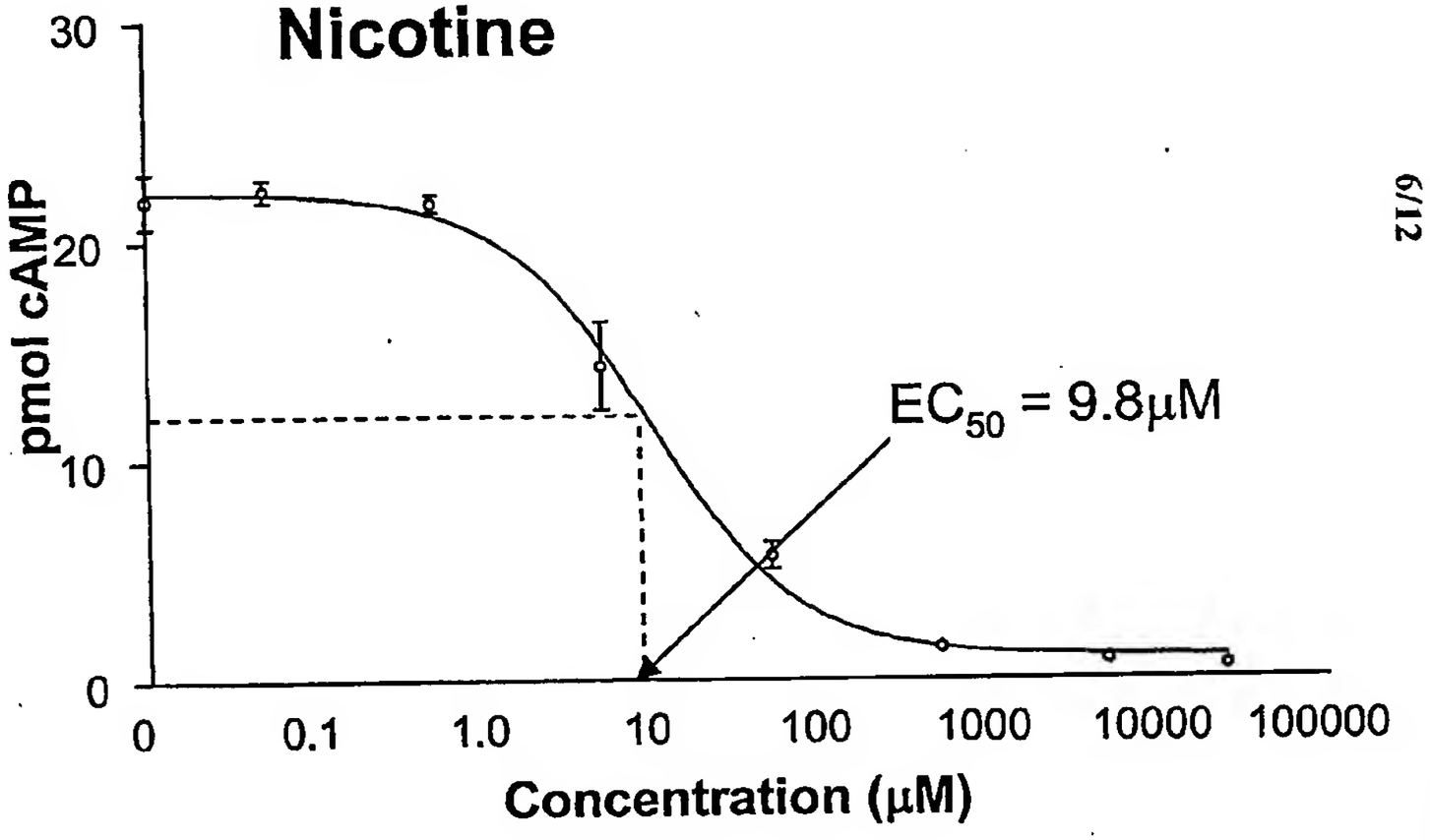


Figure 6
hRUP25 and mRUP25 inhibit TSHR induced-cAMP accumulation following activation by nicotinic acid

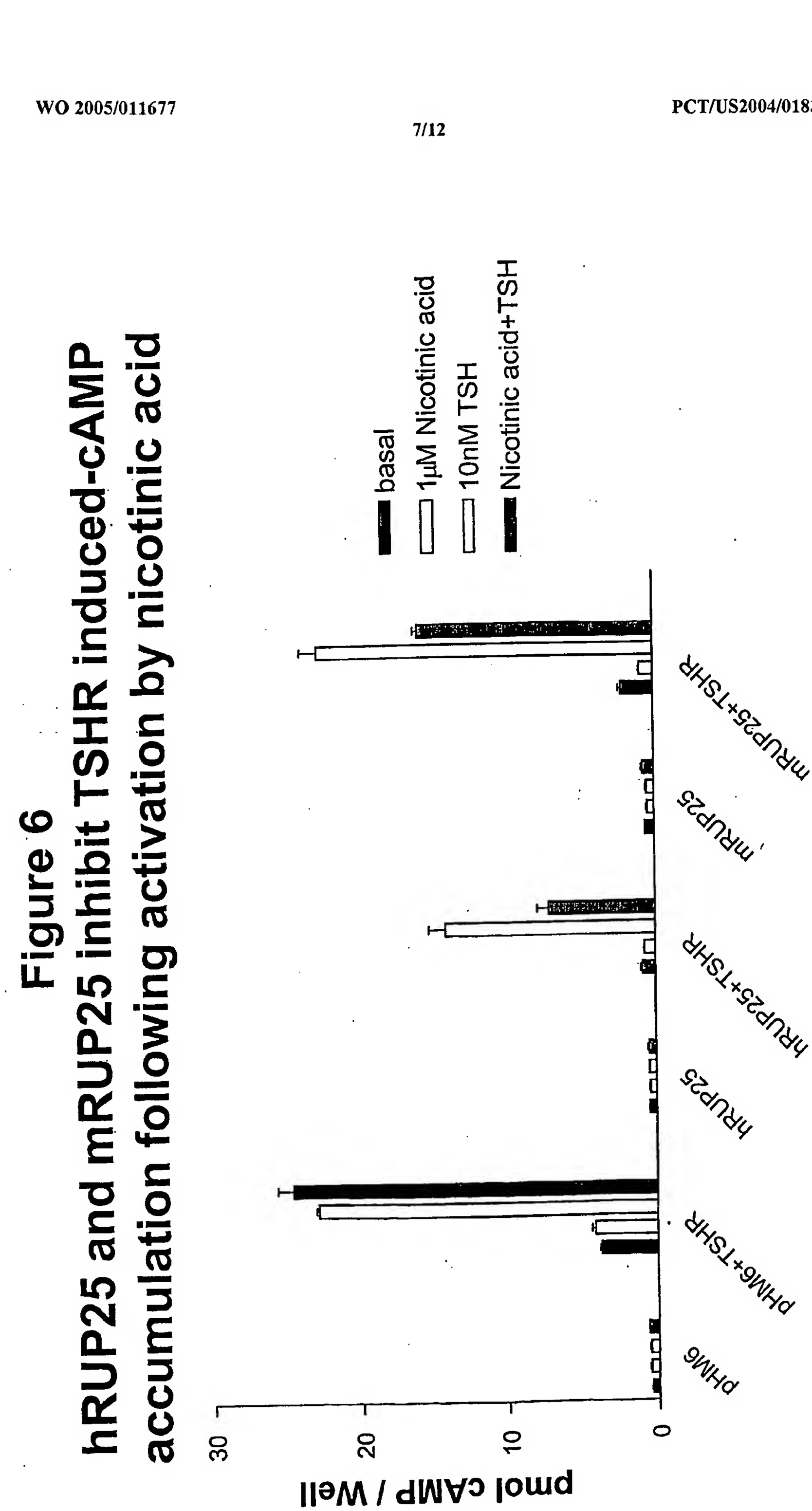
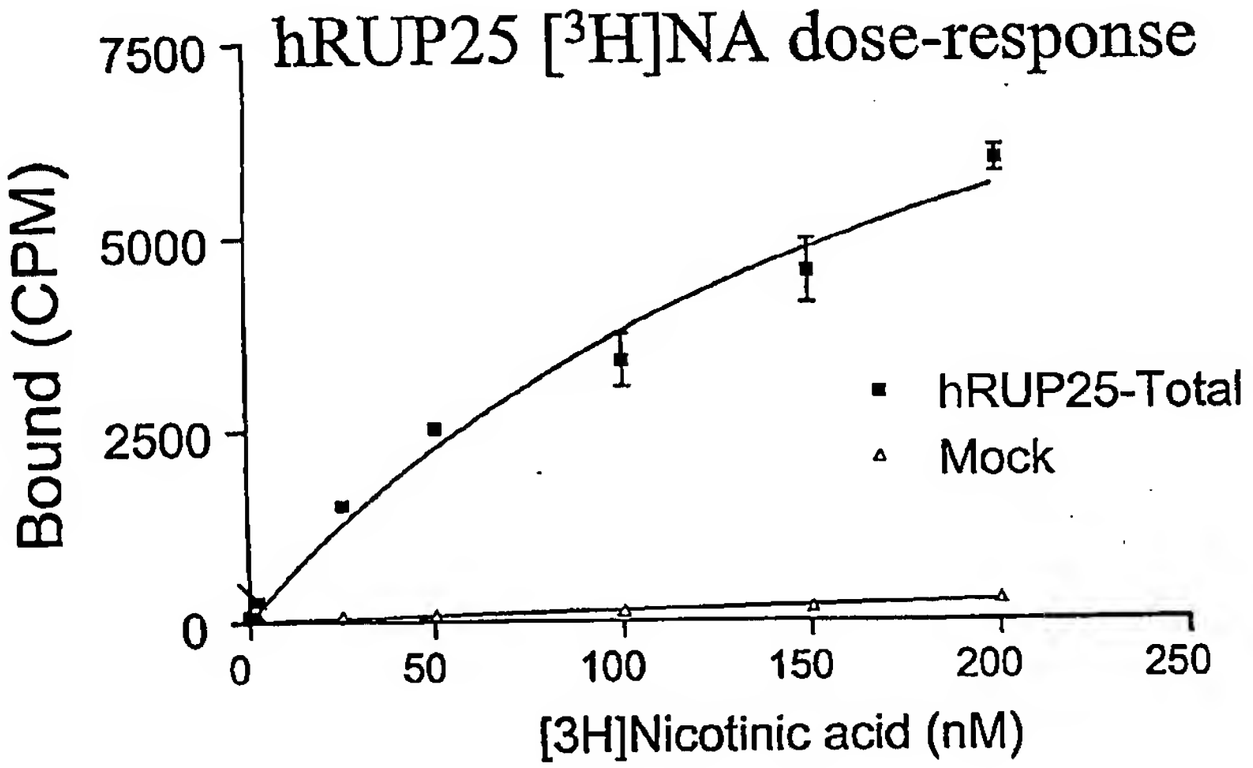
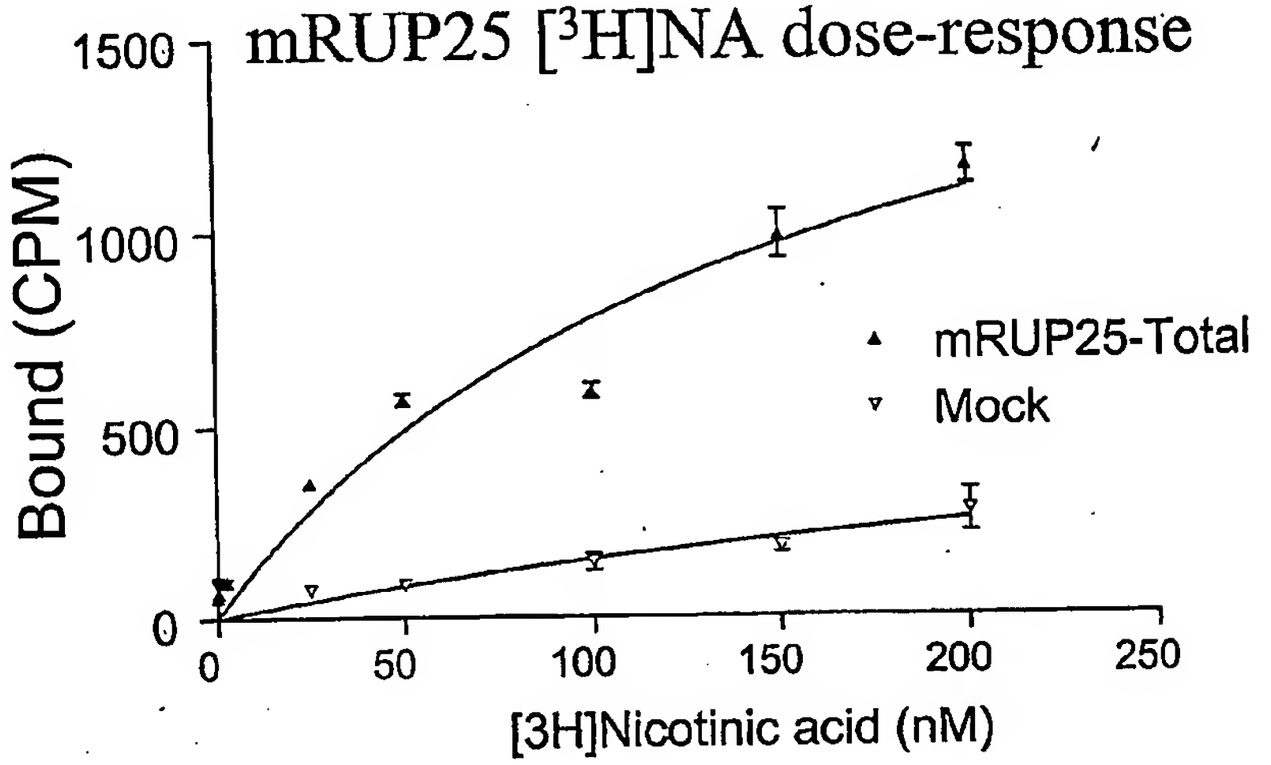
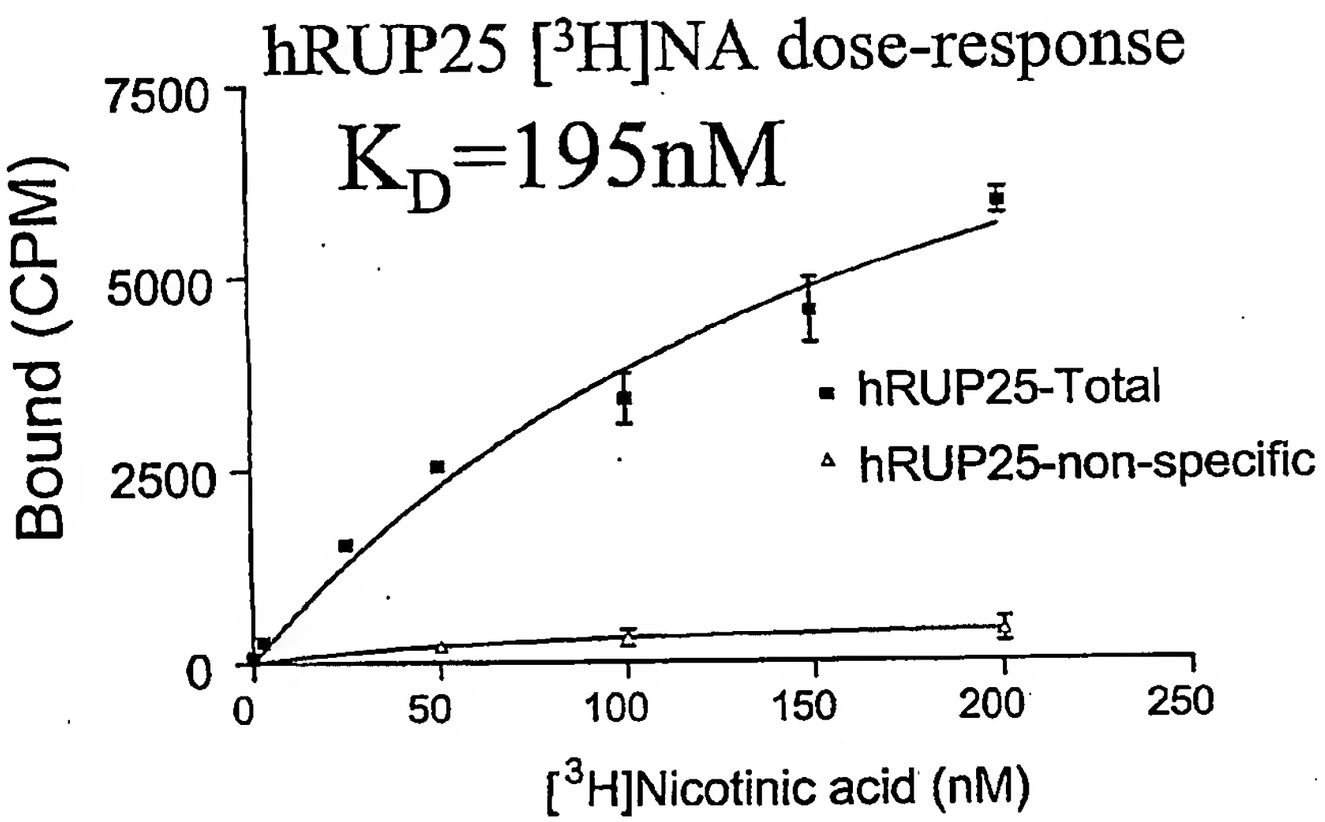


Figure 7
hRUP25 and mRUP25 bind to nicotinic acid specifically and with high affinity







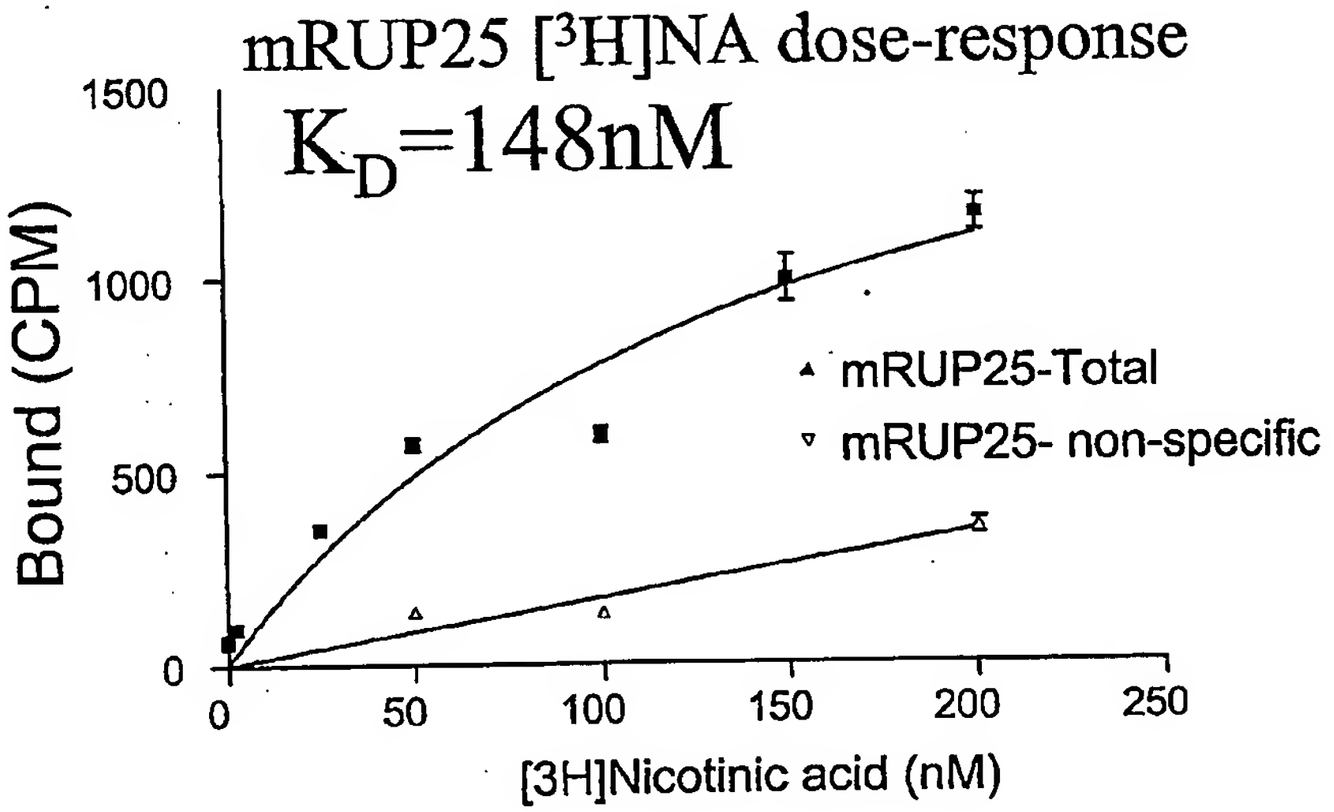


Figure 8

The rank order of potency of compounds on hRUP25 closely matches that of the pharmacologically defined nicotinic acid receptor

	EC 50 (μM)			
Compound	**Adipocytes***	**Spleen***	**hRUP25†**	**hRUP25 (K_d)‡**
Nicotinic acid	1.42	0.703	0.04	0.14
Pyridazine-4-carboxylic acid	3.76	3.14	N.D.	2.19
Acipimox	10.3	6.56	2	2.68
3-Pyridine-acetic acid	16.4	21.8	3	1.64
Pyrazine-2-carboxylic acid	26	22	4	4.14
5-Methylnicotinic acid	30.2	30.0	7	3.58
5-Methylpyrazine-2-carboxylic acid	52.0	14.5	7	7.36
6-Methylnicotinic acid	72.6	53.7	34	21.95
Nicotinic acid-1-oxide	80.4	73.7	120	55.25
2-Hydroxynicotinic acid	132	N.D.	130	145.4
Furane-3-carboxylic acid	142	N.D.	110	130.6
Nicotinamide	>1000	>1000	>1000	128.2

N.D., not determined.

* From Lorenzen,A. *et. al. Mol.Pharmacol.* 59 (2):349-357, 2001.

† Arena data, inhibition of forskolin-induced cAMP production in hRUP25-CHO stable line #46.

‡ Arena data, [^{3}H]nicotinic acid radioligand binding assay on membranes derived from hRUP25-CHO stable line #46.

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Figure 9A
Nicotinic acid and related compounds inhibit isoproterenol induced lipolysis in rat epidimal fat derived adipocytes

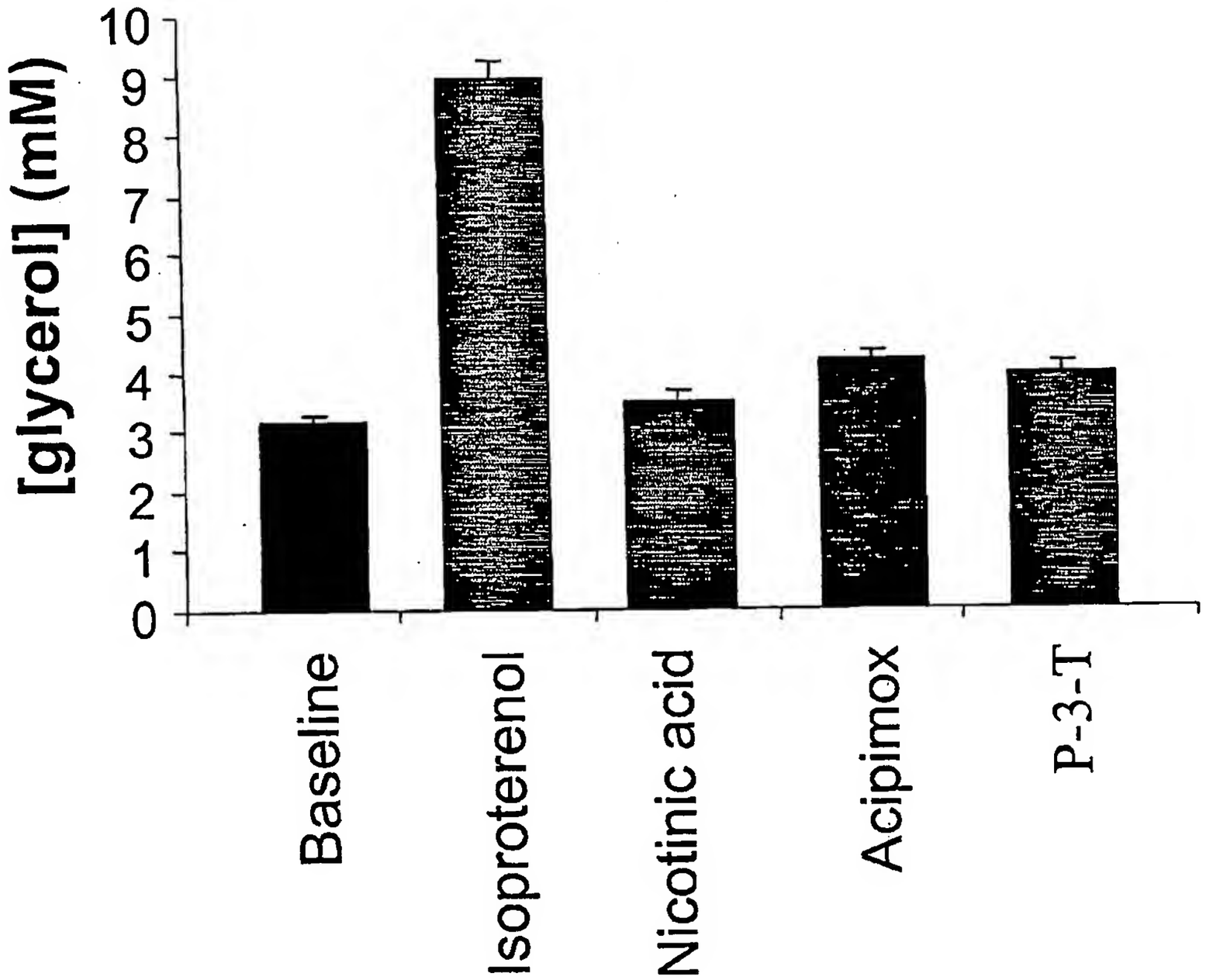


Figure 9B

Nicotinic acid dose-dependent inhibition of isoproterenol induced-lipolysis in rat, epidimal fat derived adipocytes

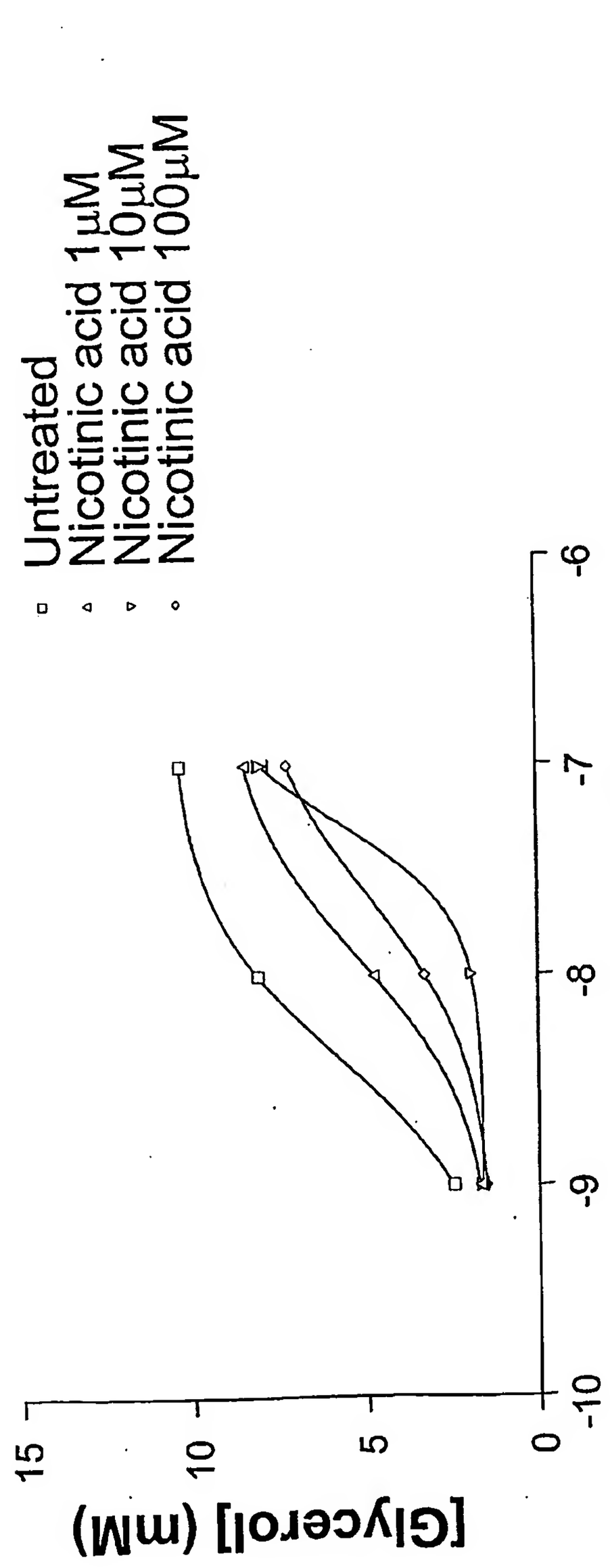
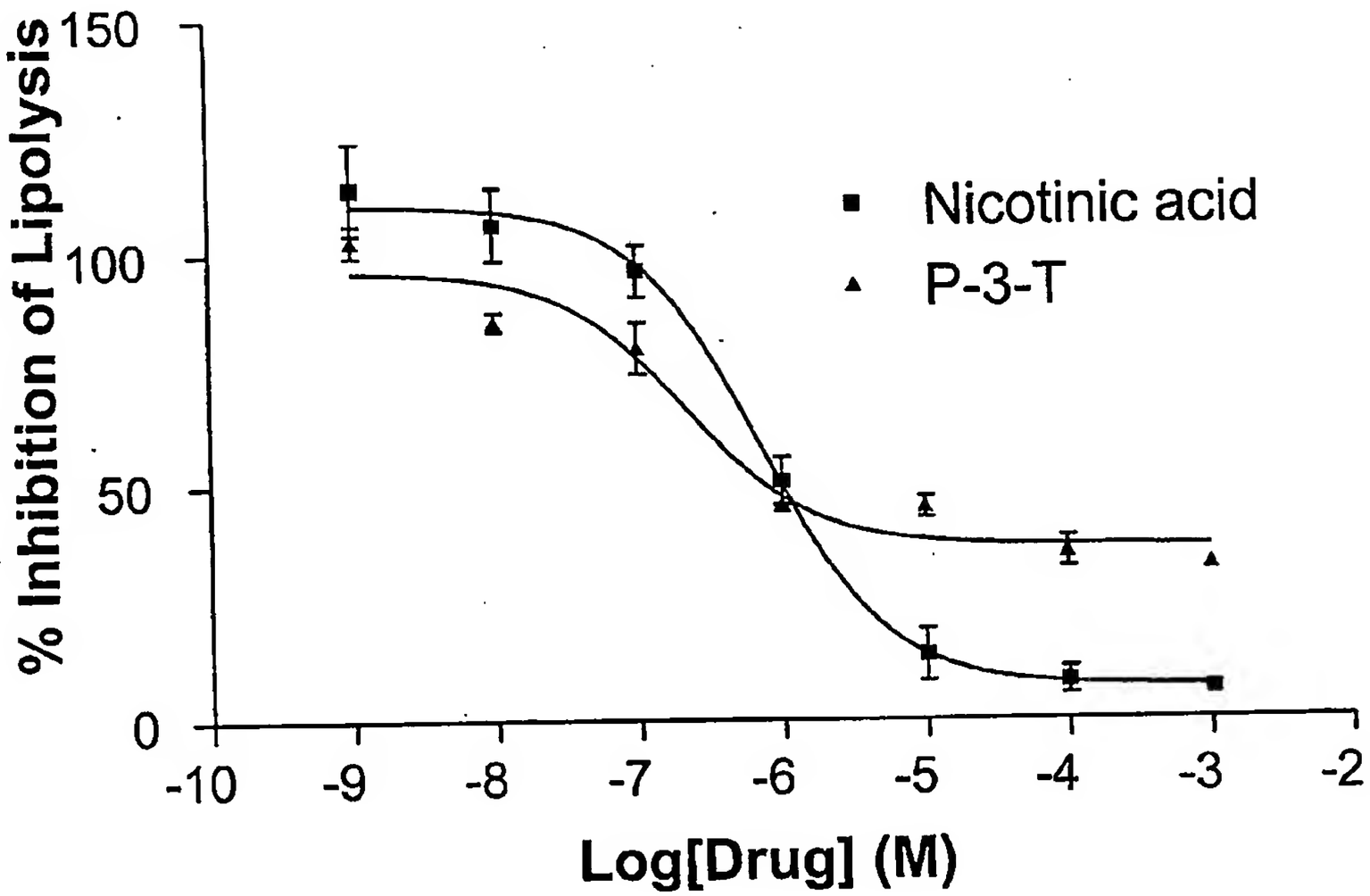


Figure 10
Dose-dependent inhibition of isoproterenol induced-lipolysis in human, subcutaneous-derived, primary adipocytes *via* nicotinic acid and P-3-T



59.WO1.ST25
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/018389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 C07D231/14 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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'A' document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2004	10/12/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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PCT/US2004/018389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 110-120 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/018389

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